Eosinophilic Esophagitis: A Novel Chronic-Inflammatory Disease of the GI Tract

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EOSINOPHILIC ESOPHAGITIS: A NOVEL CHRONIC-INFLAMMATORY DISEASE OF THE GI TRACT

Graz (Austria)
September 6 – 7, 2013

Scientific Organization:
A. Straumann, Olten (Switzerland)
A. Schoepfer, Lausanne (Switzerland)
H.-U. Simon, Bern (Switzerland)
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Session I

Basics I:
The eosinophils and the GI tract
Structural and functional barriers of the GI-tract

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Besides its important role of digestion and absorption, the gastrointestinal tract has an essential role as a major barrier against intraluminal pathogens like hostile microorganisms and toxins. This barrier function is achieved via various mechanical, chemical, and immunological mechanisms which are typically altered in inflammatory diseases thereby causing subsequent damage of the mucosa. In this review we will focus on main structural and functional barriers of host defence within the gastrointestinal tract including the epithelial layer, membrane-bound and secretory mucins, and different types of defensins. In addition we will discuss the relevance of the biofilm on the intestinal tissue and will illustrate the importance of different regulators of intestinal permeability like zonulin and desmosomal components.
Effector functions of eosinophils and immunopathology

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Although eosinophils are considered as being useful in defense mechanisms against parasites, their exact function(s) in innate immunity remains unclear. We have recently obtained evidence for a novel eosinophil-mediated defense mechanism that seems to play a role in the gastrointestinal immune system. We show that activated eosinophils are able to release mitochondrial DNA. Strikingly, the process of DNA release occurs with high speed in a catapult-like manner in less than 1 second. In the extracellular space, the mitochondrial DNA and granule proteins form extracellular structures able to bind and kill bacteria. Therefore, we called these DNA-containing structures eosinophil extracellular traps (EETs). Meanwhile, we identified EETs in multiple infectious, autoimmune and allergic diseases. Although the role of the EETs remains unclear and further work is required for better understanding of this phenomenon associated with eosinophilic inflammation and immunopathology, current observations suggest that EETs could serve as an important innate immunity mechanism protecting skin and mucosa from invasion by infectious factors.
Fibrosis and remodeling in chronic eosinophilic inflammation

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Chronic eosinophilic inflammation has been associated with tissue remodeling in a number of disease states including the hypereosinophilic syndrome (HES), asthma, and, more recently, eosinophilic esophagitis (EoE). Remodeling occurs in both the epithelial and subepithelial esophageal tissue and includes basal zone hyperplasia, epithelial mesenchymal transition (EMT), fibrosis, angiogenesis, and smooth muscle hypertrophy. Previously, research on the clinical impacts of tissue remodeling has been limited by a paucity of human tissue. However, in EoE, recurrent biopsies are required for diagnosis and management. As such, investigators are able to study the associations between tissue changes and clinical disease features. A number of pro-fibrotic and pro-angiogenic factors are elevated in EoE including TGFβ1, FGF-9, VEGF, and VCAM-1. Both eosinophils and mast cells produce a number of these factors. TGFβ1 appears to be a master regulator of end organ dysfunction in EoE and can cause esophageal EMT, fibrosis, and smooth muscle contraction. The requirement for eosinophils, the eosinophilopoietic interleukin, IL-5, and the canonical TGFβ1 signaling pathway for EoE associated fibrosis has been invoked using gene deficient mice. The clinical consequences of eosinophil associated tissue fibrosis can be devastating, such as endomyocardial fibrosis and heart failure in HES. In EoE, tissue remodeling appears to be the mechanism for multiple disease complications including esophageal rigidity, strictures, narrowing, food impactions and the clinical hallmark of dysphagia. Therapies that may be able to reduce or reverse EoE associated remodeling include topical corticosteroids, anti-IL-5, and food antigen avoidance.
Session II

Basics II:
Genetic-environmental interactions
Genetic abnormalities in EoE

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Eosinophilic esophagitis (EoE) is a complex disorder characterized by a strong eosinophilic infiltration in the esophagus. The higher prevalence of EoE in Caucasian and males noted across multiple epidemiological studies have highlighted a genetic contribution to the etiology of disease. EoE has often been noted to occur within multiple family members in a non-Mendelian pattern, indicating the heritable component of EoE is likely complex in nature. Siblings of EoE patients are substantially higher risk of developing disease, with a recurrence risk ratio of 80; these estimates suggest a 40-fold increase in disease risk when compared to siblings of asthmatic patients, where the sibling recurrence risk is 2. Although EoE is a newly diagnosed disorder involving a complex, polygenic etiology, much progress has been made towards identifying pathway involved in the disease pathogenesis and genetic variants associated with disease susceptibility. Several approaches (genome-wide and candidate gene) as well as study designs (case-control and family-based cohorts) have been utilized to begin to untangle the molecular pathogenesis and the genetic component of EoE. Here, we discuss the current molecular and genetic landscape of EoE and present the major findings, but also the major obstacles in the discovery of disease causal variants in complex disorders.
EoE and allergy in adults

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Eosinophilic esophagitis (EoE) is characterized by a T helper 2 immune reaction and often associated with elevated serum IgE levels. Most EoE patients suffer from concomitant atopic diseases, such as allergic rhinitis, bronchial asthma and/or atopic dermatitis. Allergic diseases of the airways usually precede EoE. In more than 80% of adult EoE patients, IgE sensitization to aeroallergens, food allergens or both can be detected by measuring specific IgE or skin prick test (SPT). Sensitization to food allergens such as cow’s milk, egg, fish, and seafood is less common in adult compared with pediatric EoE patients. Using component-resolved diagnostics, sensitization to food-specific allergen components can be detected in approximately 20% of adult EoE patients, whereas 70% are sensitized to crossreactive plant allergens, in particular profilins and pathogenesis-related (PR)10 proteins (birch pollen Bet v1 homologues).

The benefit of diets in the treatment of adult EoE is controversially discussed. Elimination of cereals in patients sensitized to grass pollen, wheat and rye did not improve symptoms. Six food elimination diet has been reported to induce remission of clinical symptoms. Sequential food challenge revealed cow’s milk, wheat, egg and legumes as most frequent triggers of EoE. Subsequent elimination of the offending food(s) resulted in a clinical remission of EoE up to 3 years. On the other hand, elemental diet failed to improve symptoms although tissue eosinophil numbers significantly decreased, and was not practicable in one third of patients.

The role of allergen sensitization in the pathogenesis of EoE remains to be elucidated. So far, clinically relevant diagnostic test to identify allergens triggering EoE are not available. Selective elimination of food allergens might be helpful in improving EoE symptoms.
Has elimination of exogenous allergens the potential to cure EoE?

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Recent consensus guidelines define eosinophilic esophagitis (EoE) as a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [1]. While the pathophysiology of EoE is incompletely understood, food allergens, aeroallergens and genetic factors have been implicated. A number of clinical studies have demonstrated an association between food allergies and EoE. The first study implicating food as a trigger was in children with intractable reflux symptoms and histologic changes of epithelial hyperplasia and esophageal eosinophilia despite antireflux therapy [2]. After a dietary trial removing all food allergens with an elemental formula, all 10 patients had a significant reduction in esophageal eosinophilia, 5 had complete resolution of esophageal eosinophilia, and 6 had resolution of endoscopic abnormalities. Reintroduction of the culprit foods resulted in symptom relapse in 9 of the 10 children with a median delay of only 1 hour (0.5–8 hours) after the food trigger, lending further support to this association. Specific food triggers in this group were cow’s milk, soy protein, wheat, peanut and egg. This association has been confirmed in larger series by investigators from other medical centers documenting highly effective resolution of pediatric EoE in response to elemental formula [3–5].

Since these initial studies, three strategies of dietary therapy have evolved. The first is total elimination of all food allergens with elemental or amino acid based formula. The second is a targeted elimination diet guided by allergy testing, typically skin prick testing or patch testing. The third is an empiric elimination diet removing the six most common known food groups that are triggers of EoE: soy, egg, milk, wheat, nuts and seafood [5, 6]. All three approaches demonstrate symptomatic and histologic resolution in 70% to 97% of pediatric patients in uncontrolled studies [2, 3, 4, 5]. Empiric dietary elimination has also been found to be effective in 70–75% of adults in two separate studies [7, 8]. The duration of the treatment is usually 4–6 weeks followed by a reintroduction period once remission has been achieved. Dietary therapy is therefore a reasonable alternative to topical steroids to achieve and maintain remission in both adults and children with EoE.

References:


Session III

Histology and epidemiology: EoE a new or simply a newly recognized disease?
EoE’s view through the retro-spectoscope: From case report to clinical trials

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The identification of eosinophils in the oesophagus and the correlation of these observations to a related disease process was initially slow. The first descriptions of oesophageal eosinophils were single case reports, and associated with a variety of disorders without any specific disease pattern. Single cases of achalasia, gastro-enteritis, reflux and radiologically observed strictures of unknown aetiology were described, but with no evident clinico-pathological correlation.

The first two case series were from a US based cohort (Attwood et al 1993) and a Swiss cohort (Straumann et al 1994). Both series identified that patients with high concentrations of eosinophils had a low frequency of pathological acid reflux, and a clinical pattern of obstructive dysphagia, or food bolus obstruction. Specific endoscopic features were described by Straumann in 1994. In 1995 Kelly et al described a case series in children, with a slightly different pattern of clinical presentation, where regurgitation and failure to thrive were present in younger children.

For 10 years this condition remained infrequently diagnosed. Then in 2003 the natural history of this new disease of “Esophageal eosinophilia” or “Eosinophilic oesophagitis” was described by Straumann, and specific therapy of topical steroids (Arora) and montelukast (Attwood) were introduced. Dietary based therapies (exclusion or elemental diets) were tested initially in paediatric populations, and severe cases where strictures were present were sometimes treated with dilatation.

Now with greater understanding we describe Eosinophilic Oesophagitis (EoE), with the lay term of Asthma of the Gullet, as a common, chronic relapsing inflammatory condition of obstruction to swallow, assumed to be antigen driven but without a full understanding of its true aetiology. The pathophysiology may be one of reduced compliance in the oesophageal wall in the majority of patients, rather than either stricture or muscular spasm. It is rarely life threatening but it can be the cause of spontaneous partial perforation of the oesophagus and thus have serious sequellae. It is common, and a major cause of life quality disruption. Frequently, delays in diagnosis can be the source of much physical and psychological morbidity.

Current treatments with diet, drugs and dilatation provide significant patient benefits, but a sustained specific therapy is still eagerly awaited. Randomised clinical trials are essential to assure quality in therapy. To create a suitable measure of disease benefit the creation of reliable markers of disease severity or response to therapy need to be defined.
Epidemiology (incidence and prevalence) of pediatric and adult EoE

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Eosinophilic Esophagitis (EoE) is an allergy-associated disease defined clinically by esophagus-related symptoms in combination with a dense esophageal eosinophilia, both of which are unresponsive to prolonged acid suppression with proton pump inhibitors. During the last two decades EoE was increasingly recognized in various geographical areas (mostly westernized countries) with a higher socio-economic development. The prevalence rate is increasing and reaches up to 50 patients per 100,000 inhabitants in some indicator regions. Several studies consistently demonstrate a male predominance in EoE, with a male to female risk ratio of 3:1. The average age at diagnosis ranges between 32 and 52 years and suggests that EoE is a disease of the middle aged man. It can affect patients of every race, but the disease is more common among Caucasians. Both, children and adults EoE has been clearly associated with allergies to food- and aeroallergens and most EoE patients present with a personal allergic background (e.g. asthma, rhinoconjunctivitis and oral allergy syndrome). Two emerging questions will be addressed in the presentation: 1. Does sensitization to aeroallergens influence manifestation of EoE through seasonal variation? 2. What are the implications of increased prevalence of EoE in patients with celiac disease relating to the coexistence of EoE and celiac disease? In conclusion, knowledge of epidemiologic parameters of EoE is crucial for identifying risk factors as well as pathogenic mechanisms, for planning preventive measures and for determining optimal treatment strategies.
Eosinophilic esophagitis (EoE) is currently defined as an immune-mediated chronic esophageal disorder that is diagnosed used both clinical and pathologic information. A series of consensus diagnostic guidelines for EoE have brought a measure of consistency to the field, but in practice the diagnosis of EoE can be challenging. Typical clinical symptoms of EoE, including dysphagia, heartburn, and chest pain, can overlap with gastroesophageal reflux disease (GERD), which itself is a common indication for performing endoscopic evaluation. The endoscopic findings of EoE, such as esophageal rings, strictures, linear furrows, and white exudates are not specific. Esophageal eosinophilia, the histologic hallmark of EoE, is also not pathognomonic and can be seen in a range of conditions. Further complicating the diagnosis of EoE is the newly recognized entity of proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE), a condition that must be excluded prior to confirming a diagnosis of EoE. This presentation will review the current diagnostic criteria for EoE, illustrate clinical, endoscopic, and histologic pitfalls in making the diagnosis of EoE, and highlight emerging techniques to more efficiently and accurately diagnose EoE.
**EoE: Asthma of the esophagus**

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The question whether eosinophilic esophagitis might be an asthma of the esophagus is reasonable. There are a number of similarities between the two diseases: EoE and asthma and other atopic diseases are frequently associated with similarities in their pathogenesis. Thus, investigating differences and similarities between the diseases might be worthwhile to consider.

Both EoE and asthma are chronic, immune-mediated conditions characterised by inflammatory changes in the mucosa and submucosa with a characteristic and diagnostic infiltration with eosinophils. They result in organ dysfunction with considerable morbidity and (in the case of asthma) even mortality.

Asthma and EoE affect all ages but frequently start in childhood or adolescence. While asthma has seen a large increase in its prevalence in the past 50 years EoE has first been described in the 1970s. Since then the diagnosis of EoE has increased significantly. The prevalence for both diseases seems to be highest in the Western world. In contrast to asthma, where females are more often affected, EoE is more frequent in males. Asthma in children, however, is also more common in boys but this changes after puberty. EoE is frequently associated with asthma, and up to 80% of patients with EoE are atopic, similar to childhood asthma. Adult onset asthma is not necessarily associated with atopy (termed Intrinsic Asthma) and similar observations have been made for EoE. Endoscopically asthmatic airway mucosa as well as esophageal mucosa in EoE can appear normal and biopsies are required for diagnosis. Long standing disease in asthma has been associated with „remodelling” compared to predominantly reversible, inflammatory changes early in the course of the disease. Similar observations have been made in EoE. Toxic proteins derived from eosinophils such as major basic protein, eosinophil-derived neurotoxin, can be found in the mucosa of both diseases that also have a thickening of the lamina propria or basement membrane. Despite of these histologic and immunchemistry findings, asthma as well as EoE remain clinical diagnosis and diagnosing either condition can be challenging. Therapeutically both diseases respond well to corticosteroids. Ironically, corticosteroids for inhalation are deliberately swallowed in EoE to reach the esophageal mucosa. Allergen/food avoidance can improve symptoms in asthma and EoE. Taken together allergic asthma and EoE have a number of common features which make a common pathogenesis manifested in different organs for reasons not yet fully understood likely. Combining allergological research with gastroenterologic and pneumologic expertise with a focus on similarities between these diseases might be a way forward.
Session IV

Eosinophilic esophagitis: A clinico-pathological disease?
Clinical features of eosinophilic esophagitis

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Eosinophilic esophagitis (EoE) may affect individuals at any age with a predominance for Caucasian males. The clinical manifestation of EoE is strongly age dependent. While dysphagia and food impactation are typical lead symptoms in adults and adolescents, infants often present with unspecific symptoms such as feeding problems, abdominal pain and vomiting. Some patients with EoE may experience heartburn, although rare, as the predominant symptom. Therefore, EoE should always be considered in case of heartburn refractory to medical or surgical antireflux therapy. It is important to note that both children and adults may develop behavioral strategies to avoid symptoms, which has to be taken into account in disease evaluation. The physical examination of EoE patients is usually unremarkable, however concomitant allergic diseases such as asthma, allergic rhinitis and eczema are prevalent. Up to 50% of patients may have mild peripheral eosinophilia and up to 70% may have elevated total serum IgE values.

Upper endoscopy is clearly the most important step in the diagnostic approach to EoE, however endoscopic findings are variable and none of them is pathognomonic. Frequent findings are mucosal edema with red furrows and white exsudates. Corrugated rings and strictures appear to more more common in adults than in pediatric patients. Other findings include narrow calibre esophagus and crepe paper esophagus. According to a recent metaanalysis of 100 studies including 4678 EoE patients, these endoscopic abnormalities have high specificities (90–95%) but low sensitivities (15–48%) resulting in suboptimal positive (51% to 73%) and negative (74% to 84%) predictive values. The prevalence of a normal endoscopy in EoE patients ranged from 20% in retrospective studies to 7 % in prospective studies, indicating a learning effect of endoscopists when evaluating patients with dysphagia. Based on a recent interobserver study, a novel grading and classification system for the endoscopic assessment of EoE has been proposed. Major features of the classification system are fixed rings and exsudates, semiquantitatively graded from absent to severe, and furrows, edema and strictures, graded as absent or present. Crepe paper esophagus was classified as minor feature, graded as absent or present. This classification system demonstrated a good interobserver agreement among pediatric and adult gastroenterologist with varying degrees of clinical experience with EoE, and is likely to be useful in the future for clinical research in EoE.
Histopathology of eosinophilic esophagitis

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Eosinophilic esophagitis (EoE) is a chronic relapsing antigen-driven disease, associated with characteristic histopathology of esophageal endoscopic biopsies, including alterations in the epithelium (hyperplasia, dilated intercellular spaces, surface epithelial alteration suggestive of keratinization), inflammatory cell complement (presence of $\geq 15$ intraepithelial eosinophils in at least one high power field (hpf), increased T and B lymphocytes and mast cells), and lamina propria (fibrosis). Eosinophils may form abscesses, align along the luminal surface (surface layering), and release granule-associated proteins. These pathologic changes in esophageal biopsies obtained several decades ago were attributed in all cases to gastroesophageal reflux disease, prior to the association of this pathology with disease that requires antigen-elimination for clinical and histologic improvement. Currently, the pathologic changes in EoE are characteristic but are not pathognomonic, and the differential diagnosis for esophageal biopsies exhibiting these changes includes gastroesophageal reflux disease, proton pump inhibitor-responsive esophageal eosinophilia, EoE with significant eosinophilic inflammation in other parts of the gastrointestinal tract (eosinophilic gastrointestinal disorder), and involvement of esophageal epithelium by systemic diseases such as hypereosinophilic syndrome. EoE biopsy pathology does not vary according to age or sex, among patients who have familial or sporadic disease, or between patients who have distinct clinical phenotypes such as connective tissue disorders compared to those who do not. Genetic analyses of EoE esophageal biopsies have identified a characteristic transcriptome that includes upregulation of several genes that relate to histopathology: periostin encodes an extracellular matrix protein that facilitates eosinophil migration, thymic stromal lymphopoietin influences dendritic-cell mediated allergic responses, and desmoglein is important for epithelial barrier function. Diagnostic pitfalls include the patchy distribution of the characteristic EoE pathology; examining multiple biopsies increases the disease detection rate. The method used to quantitate eosinophils including the size of the hpf influences the diagnostic yield, but excellent interobserver variability is achieved among pathologists who agree to a uniform methodology. Therapy for EoE includes diet-based approaches to eliminate offending antigens, topical steroid therapy, and novel biologic agents including monoclonal antibodies. Following appropriate therapy, biopsies may revert to normal histology, but signs and symptoms of esophageal dysfunction may persist. A potential explanation is that endoscopic biopsies obtain very small superficial fragments of tissue from an organ that has complex underlying neuromuscular components; unseen pathology in those loci may influence the clinical state of patients with normal epithelial biopsies.
Requirements of the pathologist to the endoscopist

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The diagnosis of eosinophilic esophagitis (EoE) is usually straightforward. However, the patchy nature of EoE and the overlapping histological features with GERD may obscure the diagnosis. Additional diagnostic problems may arise in patients undergoing therapy for EoE. In all these instances a close collaboration between pathologist and gastroenterologist is required. The pertinent clinical information has to be provided. The gastroenterologist should submit at least 4 biopsies from the distal and proximal esophagus, respectively for examination. Lastly, the pathologist should compare biopsies before and after treatment in patients undergoing therapy for EoE.
Value of advanced diagnostics (endo, pH/impedance, manometry, EndoFlip)

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The diagnosis of eosinophilic esophagitis (EoE) currently relies on a clinical presentation of esophageal symptoms combined with the histologic finding of eosinophilic inflammation of the esophageal mucosa. Additional diagnostic tests can (1) exclude disorders that mimic EoE, (2) identify pathophysiologic consequences of EoE and (3) improve the diagnosis of EoE. (1) Endoscopy has a fundamental role in exclusion of disorders that may present with esophageal eosinophilia including infectious esophagitis, bullous pemphigoid and eosinophilic gastroenteritis. Ambulatory pH monitoring identifies the presence of abnormal degrees of acid exposure in the esophagus that characterizes gastroesophageal reflux disease (GERD). However, GERD has a high prevalence in the general population, such that the presence of acid reflux does not indicate that the acid reflux is responsible for the esophageal eosinophilia. (2) Esophageal impedance testing has demonstrated increased baseline mucosal impedance that correlates with an increase in epithelial permeability. Increased permeability, in turn, may be an inciting event in EoE that allows for allergen access to esophageal antigen presenting cells. Esophageal manometry has not demonstrated a characteristic abnormality with sufficient sensitivity to make the test of diagnostic value in the routing management of EoE. However, manometric characteristics of esophageal pressurization and rare associated spastic esophageal motility disorder have been reported. The functional luminal impedance probe (FLIP) provides quantitative assessment of esophageal mural compliance, a physiologic correlate of remodeling in EoE. Studies using FLIP have demonstrated significant reductions in esophageal distensibility in EoE that have been linked to clinically relevant outcomes of food impaction risk. (3) The Endoscopic Reference System (EREFS) classifies and grades the severity of the five major esophageal features of EoE (Edema, Rings, Exudates, Furrows, Strictures). The EREFS has recently demonstrated acceptable inter-observer agreement and should improve the detection of subtle features while providing more uniform nomenclature to describe the endoscopic findings. Furthermore, EREFS may be useful in the evaluation of disease severity and as an objective outcome of response to therapy. The Esophageal String Test (EST) is a novel tool that utilizes a swallowed string to identify eosinophilic biomarkers. The EST has demonstrated excellent correlation with traditional biopsy derived determination of disease activity and thereby offers the promise of office based testing of inflammatory activity. Finally, reflectance confocal microscopy, multiphoton fluorescence microscopy and major basic protein ultrasound contrast agents are emerging technologies that may allow for in vivo visualization of esophageal eosinophils, thereby improving the detection and understanding of this emerging disease.
Eosinophilic esophagitis: Value of allergy tests

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Eosinophilic esophagitis (EoE) is a chronic T helper 2-type inflammatory disorder. Concurrent allergic diseases have been observed in pediatric and adult cases of EoE at a prevalence of 40–74% for allergic rhinitis, 40–70% for asthma, 4–60% for atopic dermatitis and 15–43% for IgE mediated food allergy. The observation, that EoE responds to dietary treatment and reports of intratracheal egg challenge leading in ovalbumin-sensitized mice to esophageal eosinophilia suggest that EoE is an antigen-driven process. The pathogenesis by which allergens mediate the eosinophilic disease in the esophagus needs, however, further clarification.

In immediate type food allergy diagnosis is based on a careful case history followed by a search for food specific IgE either by skin testing (SPT) or in vitro (CAP). Since detection of specific IgE does not predict the clinical response the relevance of positive IgE testing has to be proven by oral provocation testing. In children with atopic dermatitis and class I food allergy to either milk, egg, peanut, fish or wheat containing stable allergenic proteins SPT and in vitro determination of specific IgE show an excellent sensitivity of 90% to 100%. Similarly, in that special group of patients excellent negative predictive values of the SPT/CAP of up to 95% have been observed whereas the positive predictive value is low. In pollen related secondary food allergy, sensitivity of IgE testing is much lower. Due to the high rate of false negative results and the low negative predictive value of SPT/CAP using plant derived commercial food extracts, food allergy cannot be reliably excluded in that group of patients on the basis of a negative IgE testing. Consequently, oral food provocation is the gold standard of diagnosing food allergy. Similarly in EoE which does not depict the classical reaction pattern of an immediate type food allergy SPT, atopy patch test or in vitro determination of IgE to foods do not reliably predict food allergy and the average positive predictive values of these allergy tests are below 50%. Triggering foods have to be identified by elimination diet and consequent reintroduction of single foods under biopsy control.

As a conclusion: the value of allergy tests for the identification of triggering food allergens in EoE is limited. However, due to the high prevalence of allergic diseases among EoE patients, an allergy work up is urgently indicated in each patient with EoE for the diagnosis and management of associated allergic diseases.
Session V

EoE-phenotypes and assessment of disease activity
EoE in kids and in adults: One single entity or two different diseases?

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Recent consensus guidelines define EoE as a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. Adults with EoE typically present with dysphagia, food impaction and reflux symptoms while children primarily present with refractory reflux, abdominal pain, vomiting, and growth failure. Endoscopic features are also somewhat different in adults and children. Adult patients often present with fibrostenotic features of EoE including rings, strictures and narrow caliber esophagus while children present with inflammatory features of EoE including edema, white exudates and furrowing. Despite these differences in symptom and endoscopic presentation, many similarities exist within the two groups suggesting that this is the same disease in both children and adults. First, atopic history and genetic predisposition has been demonstrated in both groups. Most convincing is that both adults and children respond to food allergen avoidance implicating a common etiology in the pathogenesis of this disease. While additional data is needed to better understand the natural history of EoE, preliminary data suggests that EoE is the same disease in adults and children, but with different phenotypic presentations.
Complex relationship between EoE and GERD

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That gastroesophageal reflux and eosinophilic esophagitis may both lead to esophageal eosinophilia is well known. What is not known is how, if any, these entities interact to contribute to this pathologic entity in specific patients and how often they occur in patients as co-conspirators in disease as opposed to distinct processes. There are several hypotheses by which GERD and EoE might interact to cause esophageal eosinophilia. These include: 1. Reflux of food from the stomach with increased antigenic exposure to esophageal epithelium. 2. Reflux induced dilation of intercellular spaces in the epithelium facilitating dendritic cell and antigen movement through the mucosa. 3. A common inflammatory pathway activated by both GERD and EoE. Although these hypotheses appear plausible, supporting clinical data is not readily available. For example, it is unclear if the beneficial effect of proton pump inhibitors on esophageal eosinophilia is mediated through control of acid exposure to esophageal mucosa or independent antiinflammatory effects. There is also a lack of definitive evidence to support an increased incidence of GERD in the pediatric population in the absence of evident risk factors such as obesity. One would think if GERD were an important co-factor in this disease, the incidence of GERD would rise similarly to EoE. It is speculated that GERD and EoE co-exist and in some interact to facilitate esophageal eosinophilia and its sequelae. However, the presence and degree of this interaction likely varies remarkably. Their presence could be influenced by other factors such as age of the patient and genetic predisposition to EoE.
Determination of EoE’s activity

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Activity of Eosinophilic Esophagitis (EoE) can be assessed on the dimension of patient reported outcomes and biologic measures. Patient reported outcomes include symptoms and quality of life whereas biologic measures refer to endoscopic activity, histologic activity, biochemical activity (e.g. blood biomarkers) and “advanced technologies” such as the Endoflip device or the results of the esophageal string test. So far a validated tool to assess EoE activity in the above mentioned dimensions is lacking. Given the lack of a standardized way to assess EoE activity in the various dimensions the results of different clinical trials may be difficult to compare. Several studies in adult and pediatric EoE patients using different symptom assessment tools have reported a correlation of patient reported outcomes with endoscopic and histologic findings whereas others could not establish such a correlation. For symptom assessment in adult patients, the main symptom “dysphagia” should be evaluated according to different standardized food consistencies. Furthermore, symptom assessment should take into account the following items: avoidance of specific food categories (due to EoE problems), food modification, as well as time to eat a regular meal. A distinct recall period (such as 2 weeks) has to be defined for symptom assessment. Performing an “esophageal stress test” with ingestion of a standardized meal to measure symptom severity bears the potential risk of acute food bolus impaction and should therefore be avoided. Symptom assessment in pediatric EoE patients is even more demanding than in adults given the larger symptom variety and the difficulties to determine apart from what age patient-reported outcomes can be performed and up to what age parent-reported outcomes should be used. The description of endoscopic findings in EoE has meanwhile been standardized (Hirano I, et al. Gut 2013). Histologic evaluation of EoE activity should report either the size of the high power field used (in mm²) or count the eosinophils per mm². There is a current lack of blood biomarkers demonstrating a good correlation with histologic activity in esophageal biopsies. The development and validation of an adult and pediatric EoE activity index is urgently needed for clinical trials, observational studies, but also daily practice.
Non- and semi-invasive methods to monitor eosinophilic esophagitis (EoE)

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Monitoring inflammation associated with EoE relies on the identification of biomarkers that provide an objective measure of disease activity; to date, this has been the number of eosinophils in the squamous epithelial tissue. The search for alternative biomarkers as well as alternative methods to capture them has been the source of much research. With respect to the biomarkers, a number of candidates have arisen including peripheral blood eosinophils, eosinophil granule proteins, cytokines such as eotaxin-3, Thymic Stromal Lymphopoietin, IL-5 and IL-13, micro RNAs, leukotrienes and exhaled nitric oxide.1-8 Methods to assess these biomarkers have included blood draws, luminal lavages, breath collections and tissue analyses. Our group has utilized the Enterotest to capture esophageal contents and termed this the Esophageal String Test (EST).3 Results from these studies have demonstrated the ability of the EST to detect eosinophil granule proteins in esophageal fluid that is reflective of tissue eosinophilia. In addition, measurements of granule proteins were able to monitor for disease activity before and after standard of care treatments. Research studies using the EST have also been able to capture the esophageal microbiome, another potentially novel biomarker of disease activity.9

References:


Perspectives and requirements from the regulatory authorities

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Like many rare diseases, eosinophilic esophagitis (EoE) is a poorly understood disorder, and assessment tools to accurately determine disease activity, remission, and natural history have long been inadequate. Clinical outcome assessments and specific endpoints that can be used to assess the effectiveness of candidate therapeutic agents in clinical trials have been a particular deficiency and are urgently needed. With no approved therapy available to patients and with the prevalence of EoE increasing in children and adults, collaborative approaches to drug development involving all stakeholders are becoming ever more important. Elucidation of several parameters essential for interpretable EoE registration trials, including the need for clinically meaningful endpoints that measure changes in clinical symptoms and signs in addition to the assessment of endoscopic intraepithelial mucosal eosinophilia are critical. A understanding the natural history of EoE would inform study design, study population and endpoints. Characterizing the different EoE “phenotypes”: inflammation ± fibrosis and stricture may require different study designs/study populations, and an understanding of differing presentations in pediatric vs. adult patients. The ongoing development of Clinical Outcome Assessments by Alain Schoepfer (i.e., the EEsAI) and James Franciosi (i.e., the Pediatric EoE PRO) promises a path forward to identifying clinically meaningful endpoints. Advances in endoscopic and histologic scores including the EoE Endoscopic Reference Score (EREFS) – Hirano and the EoE Histology Score – Collins may play a pivotal role in drug development for EoE. The development and use of biomarkers, particularly, in early phase drug development, have become an important focus for investigations that might reduce clinical reliance on serial invasive monitoring. The concerted efforts of a collaborative initiative between the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition; the International Gastrointestinal Eosinophilic Researchers and the US Food and Drug Administration continue to focus on rational approaches to developing therapeutics and drug development paradigms in EoE.
Session VI

Treatment I:
Current therapeutic options (the DDD’s)
Indications for therapy

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Indications for treating EoE

At present, it is still debated whether the focus of EoE treatment should be directed towards a symptomatic or towards a histological response, or even a combination of both parameters. This question can yet not be finally answered. Nevertheless, there are at least three good reasons to treat patients with clinically and histologically active EoE:

First, dysphagia, with its ongoing risk of food impaction, has a substantial negative impact on the patient’s daily life. Despite the fact that patients often cope with their symptoms and accept even marked restrictions in their habits, they often are excited experiencing – usually beginning shortly after the start of an efficient treatment – a marked enhancement of the quality of life.

Second, untreated EoE permanently harbors the risk of long-lasting food-impactions. There is evidence that this unpleasant, unforeseeable and even risky incident can be prevented by an efficient treatment of the eosinophilic inflammation.

Third, it has been demonstrated in several clinical studies as well as in animal models that unbridled eosinophilic inflammation leads to a so called remodeling of the esophagus with wall thickening, stiffness of the organ and stricture. Prevention of esophageal damage caused by tissue remodeling is therefore another reason advocating strongly a consequent treatment.

Finally, there is some evidence that untreated EoE is a risk factor for acute infection of the esophagus with Herpes simplex virus, leading to a severe ulcerative and extremely painful esophagitis. Prevention of HSV esophagitis might be therefore a fourth indication for treating EoE.
Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder of the esophagus, that in a genetically susceptible host, is triggered by a food antigen. Emerging evidence supports impaired epithelia barrier function as the key initial event in the development of EoE and other allergic diseases. Remodeling, fibrosis and esophageal stricture formation are a consequence of persistent unbridled eosinophilic esophageal inflammation and can be potentially prevented with resolution of the esophageal inflammation. Symptom resolution, histological remission and prevention of both disease and treatment-related complications are the goals of treatment. Successful treatments include pharmacologic therapy with oral or topical steroids and dietary therapy. Elemental diet and both empiric and allergy test directed elimination diets, are dietary approaches to treatment inducing clinical and histological remission. Dietary therapy with exclusive elemental diet offers the best response with remission in greater than 96% of patients. Empiric elimination diets and allergy test directed diets offer identical response with remission-induced in three of four patients (75%). In patients who achieved clinical and histological remission with either empiric elimination diet or allergy tested diets the subsequent food re-introduction has identified cow's milk, wheat, egg and soy as the four most common food antigens likely to induce esophageal inflammation. Studies have shown that mucosal healing reverses early fibrosis and if the mucosal healing is sustained, progression and reversal of remodeling and fibrosis can be achieved. Since the remission is identical with both elimination diets and topical steroid treatments the selection of the type of treatment should be tailored to the needs of the family.
Treatment of adult EoE with diet

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The demonstration of food allergy in the origin of most cases of eosinophilic esophagitis (EOE) made possible dietary therapy by restricting from the diet those foods triggering the disease. Dietary therapy primarily emerged as an therapeutic option for pediatric EoE patients, but prospective studies developed in recent years have also demonstrated that it should be considered a feasible option for adult patients, and a non-pharmacologic alternative to topical steroids.

The limited predictive ability of allergy tests to identify food triggers in pediatric EoE also has been shown in adults: the exclusion of foods showing sensitization after skin prick tests, prick-prick tests and atopic patch tests was effective in reducing the eosinophilic infiltration below 15 eos/hpf only in 18% of adults, even when multiple foods were excluded from the diet.

The strategy of empirically removing the 6 groups of potentially allergenic foods has demonstrated an efficiency over 70% in two prospective trials, similarly to what is shown in children. Sequential reintroduction of individual foods under endoscopic and biotic control enabled the identification of the specific food triggers, by causing recurrence of a pathological eosinophilic inflammation. Milk, wheat and egg are commonly involved in adult EoE, as described in children, while the frequency for other foods showed geographical differences, probably related to distinctive cultural habits determining staple diets, or specific patterns of sensitization in different geographic areas. Relevantly, the continuous avoidance of those foods triggering EoE associated with prolonged remission of the disease.

The presence of heartburn as the predominant symptom was identified as a possible predictor of response to elimination diets; however, duration of symptoms, personal or family history of atopy, density of eosinophilic infiltrate, or endoscopic features showed no differences between patients responding and not to the empirical elimination diet. Indeed, different approaches for the dietary management of adult EoE patients may be possible, but to date we have no predictors that allow us to identify profiles of patients candidates to different interventions.

A recent research has demonstrated that exclusive feeding with an elemental formula is equally effective in adults and children with EoE; However, a large proportion of patients abandoned the study protocol due to intolerance. Any case, the high proportion of adult patients sensitized to profilin, a panallergen shared by multiple plant foods that are not excluded from empiric elimination diets could explain the lower effectiveness of the latter compared to elemental diets.

The long-term success of exclusive dietary therapy adult EoE would require the simplification of dietary interventions and the effective replacement of foods that must be definitively excluded.
References:


Treatment of EoE with drugs 1: Corticosteroids

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Eosinophilic esophagitis (EoE) is defined as a chronic immune-antigen- mediated esophageal disease characterized by clinical symptoms of esophageal dysfunction and histologically by eosinophil predominant infiltration. Treatment of EoE should therefore lead to improvement of clinical symptoms and histological decrease of eosinophilic inflammation. Reduction of symptoms are an important aim of EoE therapy, since in several studies histologic and symptom response could show a good correlation.

Topical corticosteroids (fluticasone, budenoside) have demonstrated to be effective in treating EoE and therefore they are first line therapy. Until now there is no approved therapy in the world for EoE. This is the reason why EoE patients are treated with medication available as inhalers or aqueous nebulizer solutions, which have to be swallowed. After administration patients are not allowed to eat or drink for 45 min in order the esophagus is well coated and topical anti-inflammatory effect is maximised. For adults different dose ranges are existing: Fluticasone 440–880 mcg/day twice daily, Budenoside 2 mg/day divided dose for inducing remission over a period of 8 weeks. Since EoE is a chronic disease with relapsing character after termination of the medication, a maintenance therapy seems to be valuable, but there is no evidence in controlled studies with long term follow up. In several randomized trials both topical corticosteroids could show a good safety profile. Oral candidiasis is presenting the most common side effect of topical steroid therapy. At the moment no data about long-term safety in EoE are available.
Eosinophilic esophagitis (EoE) represents a T-helper (Th)2-type inflammatory disease. Besides corticosteroids, which are not covered here, non-corticosteroid drugs have also been tested in EoE within clinical trials, including CRTH2 antagonists as well as proton-pump and leukotriene inhibitors. Anti-IL-5 and anti-TNF-alpha antibodies have also been used. While anti-eosinophilic activity has been observed in almost all patients treated with anti-IL-5 antibodies, proton pump inhibitors and CRTH2 antagonists reduced esophageal eosinophilia in subgroups of patients only. In some, but not all cases, anti-eosinophilic activity was associated with clinical improvement. Anti-TNF-alpha antibody or leukotriene antagonist treatment did not reduce eosinophil infiltration of the esophagus. Results of investigator-driven studies will be presented.
Treatment of EoE with dilation

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Treatment options for EoE include drugs, diets and esophageal dilation. Esophageal dilation can be performed using either through-the-scope balloons or wire-guided bougies. Esophageal dilation can lead to long-lasting symptom improvement in EoE patients presenting with esophageal strictures. Esophageal strictures are most often diagnosed when the 8–9 mm outer diameter adult gastroscope cannot be passed any further or only against resistance. Relying purely on the endoscope-dependent assessment of esophageal diameter may lead to underestimation of the presence of low-grade strictures (e.g. with a diameter of 12–13 mm) which may also contribute to EoE symptom generation. Alternatives to assess esophageal diameter include the use of inflatable balloons with defined diameters or the Endoflip device. A defined esophageal diameter to be targeted by dilation is missing but the majority of patients has considerable symptomatic improvement when a diameter of 18mm has been reached. A high complication rate, especially regarding esophageal perforations, has been reported in small case series until 2006. Several large series were published in 2007 and later that demonstrated that the complication risk (especially esophageal perforation) was much lower than what was reported in earlier series. The procedure can therefore be regarded as safe if some simple precautions are followed. Esophageal dilation does not influence the underlying eosinophil-predominant inflammation. Patients should be informed before the procedure that post-procedural retrosternal pain may occur for some days which usually responds well to over the counter analgesics such as paracetamol. Dilation-related superficial lacerations of the mucosa should not be regarded and reported as complications but rather represent a desired effect of the therapy. Patient tolerance and acceptance for esophageal dilation are reported to be good.
Session VII

Treatment II:
Current therapeutic concepts and future options
Eosinophilic esophagitis (EoE) impacts patients’ nutritional well-being and quality of life with complications that include food impaction and esophageal perforation. EoE therapies are rapidly evolving as the mechanisms underlying the disease become better understood. Diet therapies designed to remove specific food allergens inciting the inflammatory cascade are highly effective. While conceptually attractive, the need for repeated endoscopy with biopsy remains a major drawback. Pharmaceutical agents for the indication of EoE are in the early stages of development. At this time, the most significant therapeutic efficacy has been demonstrated with the use of topical, swallowed corticosteroids. The benefits of these agents have been convincing in terms of tissue inflammation. Symptom benefits have been more difficult to demonstrate, possibly due to limitations in available patient reported outcome instruments as well as symptom-pathology dissociation related to esophageal remodeling. While corticosteroids are a frontline therapy for EoE children and adults, increasingly recognized are a subgroup of EoE patients who are either refractory or chronically dependent upon topical corticosteroids. Studies involving therapies targeting specific immunologic targets in the pathogenesis of EoE offer great promise but currently have demonstrated significant but modest histologic improvement. Potential benefits of this approach include avoidance of long-term corticosteroids and ability to act as disease modifying agents. Therefore, systemically acting therapeutic agents may offer greater disease benefits than topically acting agents. Therapeutics under development for EoE that target inflammatory pathways have less clear short-term benefits in terms of reversing preexisting remodeling consequences. It may, therefore, be inappropriate to expect short-term use of anti-inflammatory agents to adequately address the fibrostenotic complications of EoE. To emphasize this point, the most rapidly effective treatment for dysphagia in adults with EoE is endoscopically guided, esophageal dilation. Dilation, however, does not address the underlying inflammatory process that resulted in the development of fibrostenosis. Reduction in esophageal inflammation rather than symptom relief may, therefore, be a more appropriate primary endpoint of the therapeutics currently in development. While this paradigm is yet unproven, the current emphasis on symptom outcomes recognizes the contribution of remodeling effects but deemphasizes anti-inflammatory effects. Utilization of the most accurate therapeutic endpoints is essential to avoid overlooking valuable treatments for this important and growing disease.
Management of refractory eosinophilic esophagitis (EoE)

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Whereas most children and adults respond to traditional EoE treatments, such as exclusion of dietary allergens or the use of topical steroids, a small fraction may not. The approach to this type of patient continues to evolve and decision-making should consider a number of issues including the patient’s age, lack of our complete understanding of natural history of disease, risks of assessments and side effects of treatments. Next one will need to define the term refractory, does this mean that a patient’s symptoms are persisting or that esophageal inflammation persists despite diet or drug treatment. Before considering alternative treatments, it is important to rule out any other cause of persistent symptoms. For instance, could they be related to an occult esophageal narrowing that was not identified at the time of endoscopy? Esophagrams may be necessary to identify localized or longitudinal narrowing that could be amenable to dilation. If symptoms and inflammation are persistent and no narrowing is appreciated, an elemental diet can be considered but the long term use of this in older children and adults may be difficult. Prednisone or systemic steroids may be indicated to induce a remission but side effects and complications associated with chronic use are limiting. Finally, the use of immunosuppression or biological has been reported in case reports and studies; use of these may be limited by side effects or if available, compassionate use protocols. As the scope of esophageal eosinophilia continues to evolve, the identification of new clinical phenotypes will be important to carefully characterize clinically and molecularly so that new therapeutic targets can be identified.
Future therapeutic options

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Currently, the treatment modalities for EoE include the 3 Ds, drugs (corticosteroids, PPI, leukotriene antagonists, CRTH2 blockers, immunosuppressants and biologic agents), hypo-allergic diets, and finally esophageal dilation. Drugs have the limitation that only corticosteroids have proven efficacy, whereas the majority of the other compounds have only limited or even no effect. Diets interfere severely with the quality of life, have some risks for malnutrition and need to be maintained likely for an unlimited time period. Dilation provides a rapid relief of symptoms, but does not reduce the underlying inflammation. There is therefore an urgent need for alternative therapeutic options.

Currently, a new generation of CRTH2 blockers with more than 100 fold higher in vitro activities than the first generation ones, small molecules blocking the CCR3 receptor (eotaxin receptor) and biologicals targeting the cytokines IL-13 and IL-4 are under evaluation. However, the efficacy of all of these compounds needs to be determined properly in randomized controlled trials, before these modalities can be recommended for clinical use. Regarding the dietary approach, a 4-food elimination diet seems to be as efficient as the established 6-food elimination diet and is likely somewhat easier to adhere.
Unmet diagnostic needs in eosinophilic esophagitis

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Great advances have been made in understanding eosinophilic esophagitis but unfortunately there are several basic aspects of diagnosis in this disease that remained unresolved. The first area of diagnostic controversy is in our ability to distinguish eosinophilic esophagitis (EoE) from gastroesophageal reflux disease (GERD). Although numerous clinical, endoscopic, histologic and serum markers either alone or in combination have been used to distinguish these two entities, a gold standard may not be identified. Whether this represents an overlap of similar pathophysiology or the frequent combination of both diseases in an individual is unclear. Genetic markers hold promise though are not seen in a majority of patients and may not account for disease derived from genetic variations or a polygenic disease. Another important unmet diagnostic need is the ability to identify food allergens that lead to esophageal eosinophilia in individual patients. The sensitivity and specificity of RAST, skin and patch testing has been demonstrated to be reliable in only a few specialized allergy centers and is a reliable tool in general practice. As a result, the only means currently of identifying specific food allergens is through procurement of tissue or eosinophil markers by invasive or semi-invasive means between food addition and withdrawal trials. This can be tedious with up to ten endoscopies performed in one study. Finally, an unmet diagnostic need is the prediction of phenotype and determination of prognosis in patients with EoE. It is likely, similar to inflammatory bowel disease, that in time we will come to understand and potentially predict the diverse presentations and course of EoE. This will be essential to determine the need for strength of initial and long term therapy and responsiveness to steroid and/or diet exclusion therapy.
Unmet therapeutic needs

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Eosinophilic esophagitis (EoE) is a chronic antigen mediated disease commonly triggered by foods. Currently the best studied and most successful EoE therapies include antigen elimination and topical corticosteroids. Additional interventions that have been utilized in EoE include biologics such as anti-IL-5 and -13 as well as inflammatory cell receptor blockade with CRTH2 antagonists. These therapies have met with varying success. Despite the availability of effective EoE treatments, a number of unmet therapeutic needs remain. Firstly, chronic EoE-associated inflammation gives rise to a number of complications including esophageal narrowing, rigidity, and strictures. The current data suggest that fibrosis and esophageal width can improve following therapy in a subset of subjects. However those patients who are most likely to benefit from therapeutic interventions and the subset of subjects in whom a natural history to stricture formation could be altered by therapeutic interventions remains to be fully understood. In addition, the relative reversibility of fibrosis in children versus adults requires further study. This may impact both the timing and duration of interventions. Secondly, although it is clear that EoE is a chronic disease in both adults and children, the dose and role of maintenance therapy remains to be elucidated, especially in children. In the context of diet, possible interventions for inducing food tolerance require controlled trials in EoE. Thirdly, the potential role of combination therapy needs to be systematically investigated. Finally, an understanding of pharmacogenomics in EoE could be of significant utility for predicting the likelihood of therapeutic response to a specific intervention.
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POSTER ABSTRACTS

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Comparison of demographic and endoscopic features with pH metric findings in patients with gastroesophageal reflux symptoms

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Introduction: GERD is a common condition with troublesome symptoms and high clinical impact. Although it is not the gold standard, combination of pH metry with endoscopic findings is valuable in evaluating the presence and degree of reflux. We investigated the correlation of demographic (age, gender, BMI) and endoscopic features (presence of hiatal hernia, esophagitis and H. pylori) with DeMeester scores and symptom indices.

Methods: Hundred and sixty-six consecutive patients with reflux symptoms that underwent 24 hour pH metry were evaluated retrospectively. Age, gender, BMI, endoscopic features (presence of hiatal hernia, esophagitis and H. pylori) were recorded in addition to pH metric findings (DeMeester scores and symptom indices namely SSI, SI and SAP).

Results: There were 166 patients (70 male, 96 female) with mean age 45.6 years and mean BMI 26.7 kg/m² [range 15.5–41.1]. Endoscopic evidence for esophagitis and hiatal hernia were found in 12.6% and 16.8% of the patients, respectively. DeMeester scores and symptom indices were significantly higher in patients with esophagitis of all grades and in patients with hiatal hernia. No relation was found between pH metry parameters and BMI. DeMeester scores and symptom indices did not differ in patients with or without H. pylori. DeMeester scores, SSI and SAP significantly increased with age.

Discussion/Conclusion: In this study age and hiatal hernia were the only two variables seriously affecting the pH metry parameters. Probably due to cummulation of hypersensitive esophagus or functional dyspepsia in younger ages DeMeester scores, SSI and SAP increased with age. In contrary to the literature no correlation was found between BMI and acid reflux, this may be due to high percentage of regurgitation in Turkish patients rather than pure acid reflux.
Effect of four food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis

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Introduction: Eosinophilic esophagitis (EoE) is a chronic allergen/immune-mediated esophageal disorder triggered by food antigen(s). A six food elimination diet (SFED) is effective in inducing histologic remission in children with EoE. We evaluated the efficacy of a four-food elimination diet (4-FED) eliminating the four most common EoE triggers, milk, wheat, egg and soy, and compared results to SFED in subjects with EoE.

Methods: Prospective clinical trial of children with EoE who underwent endoscopic esophageal biopsies 6 weeks following 4-FED. The primary study endpoint was improvement in histology (peak eos < 15/hpf). Remission was described as complete (≤5/hpf), near complete (≤10/hpf) and partial (<15/hpf). Responders underwent sequential endoscopy with biopsies after each food re-introduction. Symptoms and endoscopic features (EREFS) before/after treatment were recorded.

Results: 24 children (71% male, mean age 9.3 years) completed 4-FED. 75% demonstrated histologic remission (<15/hpf) and have begun food re-introductions. Mean pre and post-treatment peak eosinophil count of responders were 66/hpf and 6/hpf. Complete, near complete and partial remission was induced in 33%, 39% and 28% of subjects respectively.

82% of subjects demonstrated improvement in visual findings. Improvements included exudates (86%), rings (71%), edema (42%) and furrows (33%). Presenting symptoms included vomiting (42%), abdominal pain (42%), slow eating (33%), gagging (33%) and dysphagia (29%). 54% of patients had symptom improvement following 4-FED.

Seven patients completed the food reintroduction process. Milk induced inflammation in 6 and in 2 of these wheat and soy also induced inflammation. One subject completed reintroduction without disease recurrence.

Discussion/Conclusion: 4-FED induced clinical and histologic remission in children. Preliminary data demonstrates 4-FED when compared to SFED: 1) was as effective in inducing histological remission, 2) simultaneously eliminated fewer foods, 3) required shorter duration to complete re-introductions and 4) required fewer endoscopies. These findings support continuation of our multicenter prospective study to determine the efficacy of 4-FED.
A novel minimally invasive esophageal string test measures changes in mucosal inflammation in pediatric eosinophilic esophagitis during treatment

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Introduction: Endoscopy with biopsy is currently the only method to assess disease activity in eosinophilic esophagitis (EoE). Children require multiple endoscopies, during treatment with food elimination/reintroduction, an invasive procedure that is burdensome to families in both cost and lost days of school/work. We recently reported the Enterotest, a minimally invasive string-containing capsule, can be used to quantify esophageal eosinophilic inflammation in children with EoE. This minimally invasive Esophageal String Test (EST) may be a useful tool to monitor disease activity in EoE. We hypothesize that the EST can be used to follow esophageal inflammatory changes that occur during EoE treatment.

Methods: Secondary data analysis was performed following our prospective EST trial to identify longitudinal changes in eosinophil biomarkers in subjects performing multiple ESTs. Our analysis identified 5 children that performed an EST (ranging 1–12 h) at least twice at Ann & Robert H. Lurie Children’s Hospital of Chicago. All subjects were on a food elimination diet for treatment, requiring multiple endoscopies to determine causative food(s) antigens. Eosinophil-derived granule protein (EDGP) biomarkers were measured by ELISA in string and biopsy extracts, providing correlations between string and biopsy biomarker levels with the gold standard peak eosinophil counts performed on esophageal biopsies.

Results: Four EDGPs, MBP1, CLC/Gal-10, EDN and EPX were measured in both EST samples and biopsy extracts. Each biomarker showed correlation with EoE disease status, with levels increased with active disease (≥ 15 eos/hpf) and decreased during disease remission (< 15 eos/hpf) (Fig. 1–4).

Discussion/Conclusion: Despite the small sample size, the EST and EDGP biomarkers highly reflect response to treatment, demonstrating significant changes over time in the same patient. These findings warrant continuation of our multicenter prospective study designed to determine the EST’s capacity to work in a longitudinal manner to determine disease status in response to treatment in EoE.
Dietary treatment effects in expression mast cell genes in esophagus and duodenum in EoE adult patient

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Introduction: Eosinophilic esophagitis (EoE) characterizes by the presence of dense infiltration of the esophageal epithelium by both eosinophils and mast cells. The role of mast cells in the disease and the effect of dietary treatment on its presence have not been evaluated. This study aims to evaluate changes in the mast cells' density and in gene expression of tryptase (TPSB2), chymase (CMA) and carboxipeptase-A3 (CPA3) esophageal and duodenal mucosa of EoE patients induced by dietary treatment.

Methods: Esophageal and duodenal mucosal samples from 10 adult EoE patients were obtained before and after 6 weeks of treatment with a six-food elimination diet (SFED). Samples from 10 normal controls were also analyzed. RNA was extracted using miRNA Isolation Kit (Ambion) and retrotranscribed to cDNA. Cellular counts were determined by immunohistochemistry and gene expression was assessed by qPCR using specific primers.

Results: The esophageal density of mast cells was significantly higher in EoE patients than in controls, and decreased after dietary treatment. All mast cell genes were upregulated: CMA and TPSB2 more than 3-folds, showing CPA3 a 1.7-fold increase, compared to controls (p < 0.05). Dietary treatment significantly down-regulated the expression of all genes to the control levels (p < 0.05) (Fig. 1). Changes in mast cell density or gene expression was not documented in duodenal biopsies.

Discussion/Conclusion: EoE is associated with esophageal, but not duodenal, mast-cell mucosal infiltration and upregulation of tryptase, chymase and CPA3 gene expression. SFED diet restores cell density and gene expression into normal.
Fig. 1: Mast cell gene expression in esophagus and duodenum
TLRs expression in eosinophilic esophagitis and changes after dietary treatment

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¹Research Unit, Hospital General Mancha Centro, ²Molecular Genetics Service, La Paz University Hospital, ³Department of Gastroenterology, Hospital General de Tomelloso, Tomelloso, Spain

Introduction: Toll-like receptors (TLRs) are a subfamily of pattern-recognition receptors that detect specific pathogen-associated molecular patterns (PAMPs). They constitute a link between innate and adaptive immunity. To date, no study has evaluated the role of TLRs in EoE. The aim of this study is to determine gene expression of TLRs in esophageal and duodenal mucosa of EoE patients, compared with that of controls and changes in gene expression induced by dietary treatment.

Methods: Esophageal and duodenal samples from 10 adult EoE patients were obtained before and after 6 weeks of treatment with six-food elimination diet (SFED). Samples from 10 normal controls were also analyzed. RNA was extracted using miRNA Isolation Kit (Ambion) and retrotranscribed to cDNA. TLRs expression was studied by qPCR with specific primers (TLR1, 2, 3, 4, 6 and 9).

Results: A significant upregulation in TLR1, TLR2 and TLR4 genes were documented in esophageal (being 2.5, 2.4 & 3.7 fold-increases, respectively) and duodenal mucosa of EoE patients (each one with a 1.5 fold-increase), compared to controls (p < 0.05). After dietary treatment, the expression of TLRs reduced in esophagus and duodenum, but not reaching those levels of controls (Fig. 1 & 2).

Fig. 1: TLRs expression in esophagus
Fig. 2: TLRs expression in duodenum

Discussion/Conclusion: Gene expression of TLR1, TLR2 and TLR3 was upregulated in the esophagus and duodenum of EoE patients. Dietary treatment reduced gene expression levels but not reaching that of control. TLRs are suggested to be involved in EoE pathophysiology; further studies are needed to uncover its specific role.
The absence of eosinophilic esophagitis in a large cohort of patients with gastroesophageal reflux disease in Turkey

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Aim and background: Clinical experiences and preliminary reports claimed that eosinophilic esophagitis (EoE) is a very rare condition similar with the low prevalence of Barrett’s esophagus in Turkey. We extracted the data from the largest prospective endoscopic and pathologic database for GERD in terms of the rate of eosinophilic esophagitis.

Methods: Total 1790 patients with GERD (once or more heartburn and/or regurgitation in week) referred to the upper gastrointestinal endoscopy were prospectively included from 29 centers all around Turkey after completing a validated GERD questionnaire. All endoscopists were educated for the endoscopic diagnosis of different endoscopic classifications. Six biopsies were taken from all patients and evaluated in a blinded fashion by three pathologists (2 antrum, 2 corpus, 2 distal esophagus) from same center. All eosinophils were recorded and EoE was defined if more than 24 eosinophils were detected in one high power field.

Results: Mean age was 42.7 ± 13 (16–87), and 58.5% of patients were women. We detected endoscopically esophagitis 34% (1% LA-C or D), long segment BE 0.25%, short segment BE 0.8% in all patients. Only three cases were suspected for EoE at upper gastrointestinal endoscopy. Eosinophils within the esophageal epithelium reported in 53 cases (3.4%) and when those cases re-evaluated by the pathologists, none of them was classified for the diagnosis of EoE including the three cases of endoscopically suspected EoE. Number of total eosinophils was 1–14/hpf. Patients were evaluated according to the presence of eosinophils within the esophageal epithelium even without the diagnosis of EoE (table) (p < 0.05).

<table>
<thead>
<tr>
<th></th>
<th>Eosinophilic infiltration (n = 53)</th>
<th>Without eosinophilic infiltration (n = 1542)</th>
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<tbody>
<tr>
<td>Age</td>
<td>42.5 ± 14.6</td>
<td>42.3 ± 13.2</td>
</tr>
<tr>
<td>Gender M/F (%)</td>
<td>23/30 (43/57)</td>
<td>917/617 (59/41)*</td>
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<td>Alcohol consumption (+/-) (%)</td>
<td>4/49 (8/92)</td>
<td>118/1424 (8/92)</td>
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<td>Smoking (+/-) (%)</td>
<td>22/31 (41/59)</td>
<td>457/1085 (29/71)</td>
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<tr>
<td>Erosive esophagitis (+/-) (%)</td>
<td>29/24 (55/45)</td>
<td>506/1036 (33/67)*</td>
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<tr>
<td>Hiatal hernia (+/-) (%)</td>
<td>15/38 (28/72)</td>
<td>304/1238 (19/81)</td>
</tr>
<tr>
<td>Dysphagia (+/-) (%)</td>
<td>14/39 (26/74)</td>
<td>642/900 (42/58)</td>
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More eosinophils were counted in patients with EE compared to NERD patients as expected without reaching the limits for the diagnosis of EoE. Less dysphagia was reported in patients with eosinophils within the esophagus.
Conclusions: Eosinophilic esophagitis is a very rare condition in Turkey such as Barrett esophagus in a large prospective database performed on patients with GERD symptoms only. Reasons of those differences are unclear but might be related with the high prevalence of Helicobacter pylori compared to Western counterparts, different sanitation conditions. The major drawbacks of the study were the absence of proximal biopsies and the major aim was to detect the endoscopic findings of GERD not EoE.
Prevalence, clinical manifestations and endoscopic features of eosinophilic esophagitis

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Eosinophilic esophagitis (EoE) is a chronic disease characterized by esophageal symptoms in association with a dense eosinophilic infiltrate currently defined as > 15 eosinophils per high power field, which is associated with clinical and endoscopic manifestations.

Introduction: We aimed to determine the prevalence of eosinophilic esophagitis and define its clinical and endoscopic characteristics in Romanian patients.

Methods: The study included esophageal specimens obtained from January 2009 to December 2012 in the Filantropia Hospital of Craiova were reviewed and the data on clinical characteristics and endoscopic findings of patients were obtained. Patients with eosinophils > 15 per high power field were identified as having EoE.

Results: A total of 15 patients met the criteria for EoE, establishing a prevalence of 0.68%. All patients were males. Median age at presentation was 31 years (range 16–48 years). These patients presented with dysphagia (5/15, 30.0%), gastroesophageal reflux disease (GERD)-like symptoms (6/15, 40.0%), abdominal pain (3/15, 20.0%), and other (2/15, 13.3%). The most common endoscopic finding was plaques (7/15, 46.6%), and other findings were irregular Z-line (2/15, 13.3%), erosive esophagitis (2/15, 13.3%), white exudates (1/15, 6.6%), linear furrows (2/15, 13.3%), Schatzki ring (1/15, 6.6%), ulcers (1/15, 6.6%) and erythema (1/15, 6.6%).

Discussion/Conclusion: The prevalence of EoE was 0.68% in our patients. Clinicians should pay attention to patients manifested with dysphagia and GERD-like symptoms with endoscopic findings of white exudates, plaques, Schatzki ring and linear furrows.
Prevalence of eosinophilic esophagitis in children: Clinical manifestations and endoscopic findings

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Eosinophilic esophagitis (EoE) is an inflammatory disease of the esophagus characterized by significant and isolated infiltration of the esophageal mucosa by eosinophilis, associated with clinical symptoms of esophageal dysfunction, affecting children and adults.

Introduction: The objective of our study was to determine the frequency of EoE and to outline the clinical manifestations of EoE in Romanian children.

Methods: Four large regional pediatric gastroenterology centers participated in the study. A database of endoscopy reports from January 2008 till December 2011 was reviewed. A total of 15,624 esophagogastroduodenal endoscopy studies in children, aged from 3 and 18 years, were performed. Data pertaining to the children's age, gender, indications for endoscopy, clinical findings and histopathology diagnosis were made.

Results: In 63 children (22 girls and 41 boys), aged between 3 and 18 years, EoE was diagnosed. This constituted one case per 248 endoscopic studies. The most frequent symptoms of EoE differed between the younger (3–8 years old) and older children (aged 13–18 years old). Feeding aversion, vomiting and/or regurgitation were most frequently observed in the younger children, while in older children: abdominal pain, dysphagia and chest pain. Granular mucosa, longitudinal furrows and mucosal rings belong to the findings most often summer, 23% in the fall and 25% in the winter. Time between onset of symptoms and diagnosis was 104 ± 137 days (mean ± SD).

Discussion/Conclusion: EoE was diagnosed in every age, with frequency of 1/248 gastrointestinal endoscopies, more frequently in boys than in girls.
A 4-year follow-up of patients with eosinophilic esophagitis

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Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated esophageal disease characterized with symptoms related to esophageal dysfunction and eosinophil-predominant inflammation, and is a recognized as a common, allergy-associated cause of chronic esophageal symptoms affecting both children and adults.

Introduction: The objective of our study was to determine the demographic and atopic characteristics, the histopathology of all segments of the gastrointestinal tract, and the effect of therapeutic interventions on the natural history.

Methods: We conducted a retrospective analysis of a database of patients with eosinophilic esophagitis followed over a period of four years.

Results: In 27 patients with EoE, the median age of this patient group was 23 years (interquartile range 10.5–50.5), with 46% of patients under 18 years at the time of diagnosis. The male to female ratio was 5.5:1 and atopy with sensitization to environmental and food allergens in 78% and 77%, respectively, were prevalent. Patients had EoE of the proximal and distal esophagus and 75% had in addition either mucosal eosinophilia or non-eosinophilia histopathology in the stomach, duodenum and colon. EoE was chronic, with a duration of mean ± SD, 0.89 ± 0.78 years, until first resolution and was recurrent of 64% of the patients who had resolution, 78% later relapsed.

Discussion/Conclusion: Our findings suggest that eosinophilic esophagitis is a rare disorder predominantly affecting young people and is a chronic and relapsing condition, associated with atopy and sometimes with subsequent histopathology in segments of the gastrointestinal tract other than the esophagus.
Radiofrequency ablation in patients with diseases of GIT

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Introduction: Radiofrequency ablation (RFA) is a new therapeutic procedure in gastroenterology. The principle is that the part of the targeted tissue is ablated by bipolar electrode. There are several indications for RFA – Barrett’s esophagus, GAVE syndrome (gastric antral vascular ectasia) and postradiation proctitis. Our department has 3-years practical experience with RFA procedures in GIT.

Methods: The aim of the study was to introduce our experiences with RFA and the results after treatment. Two types of catheters were used for RFA: Halo 90 for ablation of smaller lesions and Halo 360 for circumferential ablation. 11 patients with Barrett’s esophagus (high-grade or low-grade dysplasia), 2 patients with GAVE syndrome and 1 patient with postradiation proctitis underwent RFA procedures. Halo 360 and Halo 90 catheters were used in Barrett’s esophagus. GAVE syndrome and postradiation proctitis were treated by Halo 90 catheter. All procedures were done in analgosedation or general anesthesia. All patients were admitted to our hospital for 24 hours observation.

Results: 20 procedures of RFA in 14 patients were done. There were 17 RFA procedures in 11 patients with Barrett’s esophagus done. (6 patients with Barrett’s esophagus underwent 2 procedures of RFA, the rest only 1 procedure). Only 1 patient after second RFA has residual Barrett esophagus, and is waiting for the third RFA procedure. 2 patients with GAVE syndrome (and with severe recurrence sideropenic anemia before RFA) is getting better and the need of blood transfusion is lower. Patient with postradiation proctitis has decreasing symptomatology of enterorragia and tenesmus after RFA and the quality of life is getting better. No severe complication were observed. All patients had mild elevation of leukocytes (blood count) and mild chest and epigastric pain for first few days after RFA.

Discussion/Conclusion: RFA is safe and quite simple method. No severe complication were observed. RFA can be used for patients with Barrett’s esophagus, GAVE syndrome and postradiation proctitis. In patients with dysplastic Barrett’s esophagus RFA is associated with high rate of complete eradication of dysplasia and intestinal metaplasia and reduce risk of disease progression.
Prediction of NBI endoscopy in diagnosis of dysplastic changes in patients with Barrett’s esophagus

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Introduction: Barrett's esophagus (BE) is premalignant condition. Intestinal metaplasia can progress through various stages of dysplasia to esophageal adenocarcinoma. NBI (narrow band imaging) endoscopy can help us to find dysplastic changes in BE and to find the patients with risk for malignancy.

Methods: The aim is to detect the role of NBI endoscopy in the diagnosis of dysplastic changes in patients with BE. To find out the ability of NBI to predict the dysplastic changes in BE, to predict low-grade dysplasia (low grade intraepithelial neoplasia, LG), high-grade dysplasia (high grade intraepithelial neoplasia, HG) compared to the histopathological assessment. Positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity of NBI endoscopy was studied. Our study was performed in a group of 82 patients with diagnosis of BE. In those patients we compared results of NBI endoscopy with histopathological assessment. Singh classification for suspected dysplastic changes was used.

Results: We suspected 27 patients for dysplastic changes based on NBI endoscopy – 24 (88.9%) of them were positive for histopathological assessment of dysplasia, 3 (11.1%) patients were negative for histopathological assessment of dysplasia. On the other hand, we found out high rate of false negative results of NBI endoscopy. Histopathological assessment of dysplasia was found out in 40 patients (34 patients LG, 6 patients HG) out of 82. Out of 34 patients with LG dysplasia (histopathological assessment) there were only 18 (52.9%) patients with positive NBI endoscopy, 16 patients (47.1%) were negative. All patients with HG dysplasia (histopathological assessment) were positive in NBI endoscopy.

Discussion/Conclusion: Positive prediction value (PPV) of NBI endoscopy for dysplastic changes in BE was 88.9%. Thus, it seems NBI is a useful and beneficial examination method for patients with BE.
The important side effects of long term medical treatment of gastroesophageal reflux disease

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Background: The majority of patients with gastroesophageal reflux disease (GERD) require maintenance treatment with the proton pump inhibitors as potent antisecretory drugs. It might bring some questions about individual safety during the long term treatment. Adverse effects such as possible increased risk of fractures, community-acquired pneumonia, and increased incidence of infectious diarrhea or development of fundic gland polyps were described in the several retrospective studies in PPI users.

Aim: The aim of this work is to describe the individual risks of the potential significant complications to the cohort of long term treated patients with gastroesophageal reflux disease.

Methods: Prospective cohort study. Set of the patients treated for GERD with antisecretory therapy more than 2 years. Registering incidence of the events such as: fractures, bronchopneumonia, infectious diarrhea, development of the fundic gland polyps and gastric cancer.

Results: The research group consisted of 251 patients with GERD on maintenance treatment. Subgroups of 115 non-erosive reflux disease, 69 reflux esophagitis, 67 Barrett’s esophagus were included. Data were available from 225 patients (64% men, age 53 ± 14). Follow-up was on average of 6 years (2–22 years), total 1280 patient-years. There were reported 17 patients with the development of fundic gland polyps (7.5%), 4 fractures (1.8%) – 3 distal radius and 1 fracture of the shank. Only 1 case reported bronchopneumonia during treatment (0.4%) and 1 case (0.4%) of the Campylobacterial diarrhoea. In our research there wasn’t reported any gastric or esophageal cancer.

Conclusion: Serious side effects of long term treatment by proton pump inhibitors for gastroesophageal reflux disease are rare. In previously published results acquired retrospectively, the patients using antisecretory drugs for different reasons than GERD could have more important role.

Supported by the project (Ministry of Health, Czech Republic) for conceptual development of research organization 65269705 (University Hospital Brno, Brno, Czech Republic).
The association between gastroesophageal flap valve function and gastroesophageal reflux symptoms, endoscopic features, Helicobacter pylori status and body mass index

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Introduction: Endoscopic investigation is usually preferred in patients with symptoms of gastroesophageal reflux disease (GERD) in clinical practice. It has been reported that grading of gastroesophageal flap valve (GEFV) function during endoscopy adds useful information in the evaluation of these patients. However, endoscopists frequently encounter patients with impaired GEFV function, but without symptoms of GERD. Therefore, primary aim of this study was to investigate relationship between GEFV appearance and reflux symptoms, secondary aims were to explore whether any association exists between GEFV and clinical diagnosis, Helicobacter pylori status, body mass index and other factors that might affect GEFV function.

Methods: 1070 consecutive patients (643 women) who had been referred for upper gastrointestinal endoscopy were enrolled into the study. Along with demographic characteristics (age, gender, tobacco & alcohol, concomitant diseases, and proton pump inhibitors), reflux symptoms including heartburn and regurgitation were gathered from each patient. The body mass index, smoking, alcohol, concomitant diseases, and proton pump inhibitors were also recorded. During endoscopic procedure, patients were assessed for the presence of esophagitis and hiatal hernia. Esophagogastric junction was inspected while endoscope in a retroflexed position and graded I to IV according to the Hill’s classification. Grades I and II were classified as normal valves and grades III and IV as abnormal valves. Biopsy specimens were obtained from each patient in order to identify presence of Helicobacter pylori infection.

Results: At endoscopic investigation, 348 patients had GEFV dysfunction as having Hill grade III & IV, 146 patients had esophagitis and 84 patients had hiatal hernia. 583 patients reported regurgitation while 507 patients had heartburn. Presence of hiatal hernia (p = 0.000), esophagitis (p = 0.000), regurgitation (p = 0.021), and body mass index (> 30 kg/m²) (p = 0.015) are independent risk factors that affect GEFV function. However, presence of heartburn (p = 0.438), Helicobacter pylori infection (p = 0.855), smoking (p = 0.446) and alcohol (p = 0.833) are not risk factors for GEFV function.

Discussion/Conclusion: Although endoscopic grading of the GEFV appearance is useful as a prognostic factor, presence of hiatal hernia, esophagitis, regurgitation and body mass index > 30 kg/m² are independent risk factors for GEFV appearance. Patients with abnormal valves (Hill grades III & IV) but without hiatal hernia, esophagitis and regurgitation should be evaluated individually by means of gastroesophageal reflux disease.
Quality of life of patients with gastrosophageal reflux disease (GERD) in Poland

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Introduction: Many research works show that gastrosophageal reflux disease is currently a significant physical and emotional burden for patients. The aim of this work is to determine how the GERD influences patients functioning in family, professional and social life.

Methods: The research was carried out in the Gastroenterology Clinic of the Pomeranian Medical University in Szczecin and involved a group of 100 patients with GERD. The Gastrointestinal Quality of Life Index (GIQLI) survey composed of 36 questions concerning five areas of patients' lives, i.e. symptoms of the disease, physical state, social functioning, patients emotions and the influence of conservative treatment on patients' well-being was conducted.

Results: The average GIQLI score was 91.53 (99.38 men and 86.50 women). The quality of life of a greater number of surveyed patients proved to be much lower than in the population of healthy people (122.6 points). Negative emotions and the need of starting a diet reduce comfort of life of patients with GERD, particularly women.

Discussion/Conclusion:
1. Men with GERD assessed the quality of life higher than women.
2. Marital status influences the quality of life with GERD. Single patients assessed the quality of life lower than patients staying in relationships.
3. Emotional sphere affects the quality of life with GERD. Nervousness and sadness as states connected with the disease have a significant negative effect on life.
4. Patients with GERD with higher education asses the quality of life higher in comparison with patients with primary, vocational or secondary education.
5. Age, place of residence and source of livelihood do not influence the quality of life with GERD.
6. The necessity to go on a diet in GERD is a factor lowering the quality of life and causes discomfort connected with treatment.
Different clinical manifestation of eosinophilic esophagitis – Case series

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Introduction: Eosinophilic esophagitis may present itself by wide range of symptoms. The way to the right diagnosis and appropriate treatment may take a lot of time with many problems due to non-specific signs of the disease and still rare knowledge about the disease in general clinical praxis. We present three cases of the disease with quite different clinical presentation and response to the therapy.

Methods: Case presentation

Results:
Case 1: 35-year-old man with long history of esophageal discomfort and dysphagia of unknown origin. Without visible stenosis of the esophagus on the endoscopy. White plaques on endoscopy previously diagnosed as the esophageal candidosis. Repetitive biopsy samples showed eosinophilic abscesses in the mucosa. Clinical response on the treatment of swallowed budesonid was achieved. There was no effect of proton pump inhibitor (PPI) itself. Long term treatment was required.

Case 2: 38-year-old man referred as a suspicious diagnosis of achalasia. Thin stenosis in the distal esophagus. Non-specific dysmotility pattern on the esophageal manometry with persistent peristaltic waves. Quite normal endoscopic finding except for typical rings and linear furrows according to the experienced view. Biopsy samples confirmed the diagnosis of eosinophilic esophagitis. Balloon dilatation together with PPI treatment was sufficient for symptomatic response.

Case 3: 31-year-old woman with asthma and intermittent dysphagia and heartburn. No visible abnormality on endoscopy. Biopsy showed eosinophilic infiltrates in mucosa. Good symptomatic response on the high dose treatment with PPI was achieved.

Discussion/Conclusion: We referred different clinical manifestations and the required treatment in small case series of the typical patients with eosinophilic esophagitis.

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Eosinophilic esophagitis in children with coexistent celiac disease

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Introduction: Eosinophilic esophagitis (EoE) and celiac disease (CD) are distinct gastrointestinal disorders characterized by specific clinico-morphological features. Although EoE and CD are usually considered to be separate, latest reports seem to indicate a likely coexistence of these two pathologies in pediatric patients. The major objective of the study was to estimate the prevalence of EoE among children diagnosed with CD in the Department of Medical Pathomorphology, Medical University of Bialystok, in the last 3 years.

Methods: Histopathological reports of duodenal biopsies performed between January 2010 and December 2012 were surveyed to identify all cases of CD. Patients with histopathological diagnosis of concomitant EoE were selected from this group. Cases of EoE were diagnosed when the biopsies revealed ≥ 15 eosinophils per high power field in the affected esophageal mucosa. Clinical symptoms observed in patients with both EoE and CD were taken into consideration.

Results: In the 3-year study period, we found 103 patients with celiac disease, 31 patients with eosinophilic esophagitis and seven (6.8% of total CD) patients with both diagnoses (2 cases in 2010, 2 in 2011 and 3 in 2012). The vast majority of EoE + CD cases (6/7) concerned boys (one in the age range of 1–6 and five in the age range of 13–18). The patients usually presented with abdominal pain and diarrhea.

Discussion/Conclusion: The prevalence of eosinophilic esophagitis in pediatric patients with celiac disease accounts for 6.8%, confirming a higher than expected prevalence of eosinophilic esophagitis as compared to the general population. The knowledge of the potential coexistence of eosinophilic esophagitis and celiac disease may contribute to better diagnosis of these conditions.
The correlation of nutritive status, body composition and symptoms in patients with gastroesophageal reflux disease

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Introduction: The assessment of all the risk factors for gastroesophageal reflux disease (GERD) is important for the accurate diagnosis and treatment, since only certain number of patients develop macroscopic changes in esophageal mucosa. Therefore link between GERD and obesity as one of the risk factors as is at present subject of scientific research.

Methods: The aim of our study was to determine correlation between GERD, nutritive status, body fat distribution, the influence of nutritive status on quality of life in patients with GERD. 101 patient was included in the study, 45 women and 56 men. All patients fulfilled the questionnaire regarding GERD-related complaints, their frequency and intensity, and their influence on overall quality of life. Nutritive status and body composition was determined by bioelectrical impedance analysis and anthropometric measurements. All patients underwent upper endoscopy.

Results: In 35 patients reflux esophagitis was seen by endoscopy – 20 grade A, and 15 grade B. In group of obese patients (body mass index – BMI > 25) macroscopic esophagitis was significantly more frequent. Reflux esophagitis was significantly correlated with BMI, trunk fat tissue, percentage of trunk fat in total body fat tissue, waist circumference and hip-waist ratio in all patients. In female patients esophagitis was in positive correlation with trunk fat tissue, its percentage in total fat and waist circumference. Esophagitis is correlated with frequency of heartburn, vomiting, belching, hoarseness, frequency and intensity of coughing, and also significantly correlated with intensity of heartburn, frequency and intensity of regurgitation, and feeling of lump in the throat. Number of symptoms is rising with BMI. In obese patients, hiatus hernia is significantly correlated with cases of esophagitis grade B. GERD complaints do not affect quality of life in total number of patients but there is correlation between BMI and sense of diminished life quality in patients with grade B esophagitis.

Discussion/Conclusion: Obesity influences onset of macroscopic esophagitis. The amount of abdominal fat tissue is increasing number and intensity of GERD symptoms and incidence of esophagitis, regardless of BMI and represents important risk factor for GERD.
Eosinophilic enteritis (EE) with ascites triggered after childbirth: An exceptional form of presentation

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Introduction: Eosinophilic esophagitis is the most common eosinophilic gastrointestinal disorder. When eosinophilic infiltration affects more distal digestive tract it’s called eosinophilic gastroenteritis (EG), a rare and recurrent condition of unclear etiology, with a very uncommon manifestation: eosinophilic ascites (EA). Its appearance during the postpartum period is an exceptional situation.

Methods: We describe a case of post-partum EA admitted in our center, and performed a literature review based on PubMed search using the Medline subheadings and keywords: “eosinophilic enteritis”, “eosinophilic gastroenteritis”, “eosinophilic ascites”, “pregnancy”, “post-partum”, “delivery”, “childbirth” and “labor”.

Results: In addition to our patient (W1), we found 3 more reported cases (W2, W3, W4).
Epidemiology: 4 Healthy women. No drugs associated with EE.
Debut: W2, W4 after first pregnancy (W4 repeated symptoms after second pregnancy). W1, W3 after second and fourth pregnancies (both of them reported mild gastrointestinal symptoms after previous gestations).
Radiological findings: Computed tomography scan: ascites and/or jejunal thickening.
Laboratory studies: Elevated absolute eosinophil count.
Treatment and prognosis: Complete response with corticosteroids. No complications about pregnancy, labor or neonate.

FIGURES AND GRAPHICS ARE PROVIDED.

Discussion/Conclusion: All women were healthy without other possible underlying causes (drugs, parasitic infections, malignancy, vasculitis) in which the gastrointestinal symptoms were repeated in each pregnancy and remain asymptomatic between them. In all cases (except one) a firm diagnosis of EE was established (clinical, analytical and pathological criteria). Response to oral steroids in tapering was satisfactory. Despite the limited scientific evidence, all these facts allow hypothesize the labor as a firm trigger of puerperal eosinophilic enteritis, apparently without any reported risk for pregnancy, childbirth and newborn.
Prevalence, clinical presentation and endoscopic findings of eosinophilic esophagitis in adult patients in a south-west region of Romania

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Introduction: Eosinophilic esophagitis (EoE) is recognized cause of dysphagia, food impaction and heartburn unresponsive to antireflux measures. Several studies have estimated a variable prevalence among adult patients ranging from 30 to 45 cases per 100,000 habitans.

Aims of study: The aim of the study is to estimate the prevalence of EoE in adult patients in the healthcare areas of the Emergency Hospital from Craiova, in a south-west region of Romania between 2006 to 2012 and to understand clinical presentation and endoscopic findings.

Patients and methods: 28 patients with EoE entered this study, between January 2006 and March 2012. Statistics analysis painted out the prevalence of male (75%); mean age was 27.8 years (SD 10.4, rank 14–51). The research protocol contained clinical and endoscopic exams. Histological examinations of esophageal biopsies was performed and eosinophil count > 15/Hpf was confirmed (per current guidelines). Mean number of eos/Hpf 51.2 (15–121).

Results and discussions: Symptoms presented before diagnosis EoE included dysphagia (89.3%), food impaction (57.3%), hearburn (31.3%) and chest pain (21.5%). Endoscopic findings included narrowing (36.5%), rings (57.6%), altered mucosal appearance (77.2%), normal esophagus (21.6%). 18 (64.3%) patients had atopic background.

Conclusions: The prevalence of eosinophilic esophagitis in our area is lower. Children and adults showed no differences in most parameters. Atopia was present at many patients. Dysphagia and/or food impaction were most frequent symptoms and rings and/or altered mucosal appearance were most frequent endoscopic findings.
Treatment with proton-pump inhibitors and budesonide is effective in adult patients with eosinophilic esophagitis

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Introduction: Eosinophilic esophagitis (EoE) has recently been recognized as a common esophageal disorder. The management of EoE consists of dietary, pharmacologic and endoscopic interventions. The approach is based on clinical experience, small controlled trials, and case series. Steroids and/or esophageal dilations were found to be most effective in term of clinical response.

Aims of study: To assess the effectiveness of long-term treatment with proton-pump inhibitors and budesonide in patients with EoE associated with atopia.

Patients and methods: 28 patients with EoE entered this study, between January 2006 and March 2012. Atopia was present at 18 patients. Before the treatment was started, all patients underwent an upper GI endoscopy with biopsies. Histological examination of esophageal biopsies was performed and eosinophil count > 15/Hpf was confirmed. After the diagnosis of EoE had been established a long-term treatment with double dose of aPPI (e.g. omeprazole 2 x 20 mg) associated with budesonide 6 mg/day for 24 weeks. Control upper GI endoscopies with esophageal biopsies were performed in 24 weeks intervals.

Results and discussions: The treatment with aPPI associated with budesonide led to a complete disappearance of esophageal symptoms in 25 patients. 2 patients underwent a successful esophageal dilatation. PPI associated with budesonide therapy was effective in all 18 patients with atopia.

Conclusions: A significant proportion of adult patients with EoE, including those with atopia, respond to PPI therapy associated with budesonide. Treatment with budesonide is well tolerated without serious side effects. The high relapse rates after the discontinuation of budesonide therapy suggest that a long term strategy is needed for a large number of patients.
Long-term efficacy of proton-pump inhibitor therapy in patients with PPI-responsive esophageal eosinophilia

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Introduction: Proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE) is a recently described phenotype distinct from eosinophilic esophagitis (EoE), but not necessarily a manifestation of gastroesophageal reflux disease (GERD). No prospective series have been reported on the long-term efficacy of PPI therapy in this subset of patients.

Methods: Prospective observational study in consecutive adult patients with PPI-REE, defined by both dysphagia/food impaction remission and < 15 eos/HPF after high-dose PPI therapy. High-dose (quadruple) therapy was defined as: omeprazole, esomeprazole or omeprazole 40 mg bid, lansoprazole 30 mg bid or rabeprazole 20 mg bid. PPI dose was then progressively tapered until symptom relapse and maintained at the lowest dose with the target endpoint of clinical remission. Follow-up endoscopy was performed at 12 months or longer on PPI maintenance-dose, with histological examination at both distal and proximal esophagus.

Results: 17 PPI-REE patients were included with a median follow-up time of 29.27 months (14–79). 15 patients (88%) were male with a median age of 29 years-old (14–58), all of them suffered from dysphagia/food impaction and 13 (76%) had heartburn and/or regurgitation consistent with GERD. Regarding the step-down process, 14 were maintained with double-dose PPI and 3 with single-dose PPI. Eleven out of seventeen (64%) remained in clinical and histologic (< 10 eos/HPF) remission during follow-up. Among six relapsers, 5 (83%) recurred with distal eosinophilia (51.4 [25–117] eos/HPF) but no proximal eosinophilia, whereas grade A reflux esophagitis was observed in 3 patients (50%) despite double-dose PPI therapy.

Discussion/Conclusion: Sustained clinico-histological remission on PPI therapy was observed in 64% of adult PPI-REE patients after long-term follow-up, reinforcing that PPI-REE is a distinct subset of EE. In contrast, 5 out of 6 relappers (83%) showed eosinophilic inflammation limited to distal esophagus and reflux esophagitis was present in 3 cases, suggesting GERD as the dominant cause of EE in some of these patients.
An optimized four-food elimination diet (dairy, gluten, egg and legumes) might be as effective as six-food elimination diet for adult eosinophilic esophagitis: Preliminary results

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Introduction: Eosinophilic esophagitis (EoE) is a chronic immune-mediated esophageal disorder triggered by food antigens. A six-food elimination diet (SFED) achieves histological remission in 70% of adult EoE patients. The most common food triggers identified have been milk, wheat, egg and soy and/or legumes, with a minor role for nuts and fish/seafood.

Methods: Prospective multicenter clinical trial in consecutive adult patients with EoE, defined by consensus guidelines. An optimized four-food elimination diet (FFED) (dairy products, gluten, egg and legumes, including soy and peanut) was designed to avoid to the maximum cross-reactivity between food allergens. All patients underwent histological re-evaluation after 6 weeks on FFED. Histological response was defined by < 10 eos/HPF. Responders underwent reintroduction of each food for 6 weeks followed by endoscopy and esophageal biopsies.

Results: Up to now, 26 adult patients (66% male, median age 35 years-old, 100% dysphagia or food impaction) have been reassessed after FFED. Sixteen patients (61.5%) responded to FFED, in whom mean eosinophil peak count decreased from 55.6 to 1.5 (p < 0.001) and from 49.12 to 1.5 (p < 0.001) at distal and proximal esophagus, respectively. All responders have started the food reintroduction process and 6 patients have successfully completed the protocol. At the present time, the most common identified food triggers have been egg (75%), legumes (50%), gluten (42%) and dairy (16%), but these are very preliminary results. Among non-responders (n = 10), 8 have initiated rescue SFED.

Discussion/Conclusion: An optimized FFED might be as effective as SFED for adult EoE patients, improving patient acceptance of dietary limitations and reducing the number of endoscopies and overall time to complete the food reintroduction process.
Proton-pump inhibitor-responsive esophageal eosinophilia correlates with downregulation of eotaxin-3 and Th2 cytokines overexpression

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Introduction: Proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE) is a recently described phenotype distinct from eosinophilic esophagitis (EoE), but not necessarily a manifestation of gastroesophageal reflux disease (GORD).

Methods: We aimed at addressing baseline eotaxin-3 and Th2 cytokine expression in patients with suspected EoE and to characterize the course of cytokines profile after PPI therapy. In consecutive adult patients with dysphagia/food impaction and esophageal eosinophilia > 15 eo/HPF, eotaxin-3, IL-13 and IL-5 were tested in distal and proximal biopsies, at baseline and after PPI therapy for 8 weeks (omeprazole 40 mg twice daily). PPI-REE was defined by < 15 eo/HPF in both distal and proximal esophagus. EoE patients (> 15 eo/HPF on high-dose PPI therapy) were offered rescue therapy with topical steroids (swallowed fluticasone nasal drops 400 µg bid) for 6 weeks.

Results: 47 patients were included, of whom 23 (46%) had PPI-REE. No differences were observed between PPI-REE and EoE patients regarding demographics, symptoms, endoscopic findings or esophageal eosinophilia degree neither at distal (54.9 vs. 68.5, p 0.22) nor at proximal esophagus (44.9 vs. 63.1, p 0.12). Baseline molecular characteristics were indistinguishable between PPI-REE and EoE at distal (eotaxin-3, 0.72 vs. 0.54 [p 0.44], IL-13, 0.012 vs. 0.017 [p 0.86] and IL-5, 0.021 vs. 0.039 [p 0.22]) or proximal esophagus (eotaxin-3, 0.46 vs. 0.78 [p 0.23], IL-13, 0.008 vs. 0.012 [p 0.33] and IL-5, 0.016 vs. 0.071 [p 0.08]). 14/24 EoE patients were given steroids, of whom 11 (78%) achieved complete histological remission. PPI therapy significantly downregulated eotaxin-3, IL-13 and IL-5 levels in PPI-REE patients in a similar way to that seen in EoE patients after topical steroids.

Discussion/Conclusion: PPI-REE is a cytokine-mediated entity, with baseline overexpression of eotaxin-3/Th2 cytokines indistinguishable from EoE. PPI therapy downregulates these molecular markers in a similar way to that seen in EoE after topical steroids.
Safety of propofol administration in adult eosinophilic esophagitis patients sensitized to egg, soy or peanut

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Introduction: Propofol administration in a fatty emulsified formulation containing egg lecithin and soybean oil is often contraindicated in patients with allergies to egg and/or soy. However, Intralipid, a fat emulsion prepared for intravenous administration with similar elements, can be safely administered in egg- or soy-allergic patients.

Methods: We aimed at investigating the safety of propofol administration in eosinophilic esophagitis (EoE) patients sensitised to egg and soy or cross-reactant foods. This was a prospective cohort study of consecutive adult EoE patients undergoing propofol-based procedural sedation. Propofol was administered by an endoscopist in all procedures excepting two 14-years old males who underwent general anesthesia. Food-specific serum IgE measurements and skin prick/prick tests for egg, chicken, soy, peanut and other legumes (including lentils, chickpeas, beans and peas) were carried out.

Results: Sixty consecutive EoE adult patients, mostly on empirical six-food elimination diet, were evaluated. Mean age was 28 years-old (14–56), with a clear male predominance (54/6, 90%). Atopy was present in 52/60 (87%) of patients, being the most prevalent allergic comorbidities rhinoconjunctivitis (75%) and seasonal asthma (61%). The rate of food sensitisation, either by blood or skin testing, was egg (41%), soy (41%), chicken (23%), peanut (52%), lentils (64%), chickpea (17%) and pea (17%). 404 upper endoscopies (mean 6.78 [3–17]) were performed (mean propofol dose 175 mg [90–282]), including 7 stricture dilations. No anaphylactic or allergic adverse events were reported excepting a transient bronchospasm in one of the 14-years old undergoing anesthesia. This patient suffered from asthma, also received ketamine and midazolam and further allergic work-up ruled out sensitisation to propofol and Intralipid.

Discussion/Conclusion: Propofol was safely administered for procedural sedation in a large series of adult EoE patients sensitised to egg, soy or cross-reactant foods. These findings may warrant further reconsideration of warning labels regarding propofol administration in egg or soy-allergic patients
Clinical manifestation and epidemiology of pediatric eosinophilic esophagitis in Switzerland: A population-based approach

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Introduction: Eosinophilic esophagitis (EoE) has been recognized as an own-standing entity in the early 1990s. The accurate population-based epidemiological data about EoE in children is currently lacking. Our objective was to determine the frequency of pediatric EoE and to describe the clinical manifestations of EoE in the pediatric population in Switzerland.

Methods: Since 2009, data from EoE patients age ≤ 16 years from all Swiss pediatric gastroenterology centres and from the Swiss EoE Database were entered prospectively into a database. Data collected included disease-specific and demographic characteristics, diagnostic measures and first-line therapy.

Results: A total of 74 patients (52 boys; 0.5–16 years of age) were included, of which 8 (11%) were diagnosed with EoE before the age of 4 while the majority was diagnosed at the age of 10 or older. We found an incidence of 1/100,000 and a prevalence of 6.1/100,000. Feeding aversion, vomiting, regurgitation and failure to thrive were most frequently observed in the younger children, while older children presented with non-swallowing-associated thoracic pain and dysphagia. Fifteen patients (20%) experienced a bolus impaction requiring endoscopic removal. Mean interval from the first symptom onset to the time of diagnosis was 2.6 years. Topical steroid treatment was the first-line therapy for 49 patients (66%). Dietary treatment was performed in 19 children (26%), whereas dilatation was performed in 6 patients (8%).

Discussion/Conclusion: In Switzerland pediatric EoE is markedly less frequently reported when compared to adult EoE (prevalence 35/100,000 inhabitants) and to pediatric data from USA (prevalence 43/100,000). Our data most likely underestimate the real incidence/prevalence of EoE. We believe therefore that in Switzerland EoE in children is under-diagnosed due to 1.) The non-specific clinical manifestation in infants, 2.) The lack of non-invasive diagnostic tools; and 3.) The higher threshold for performing gastroscopy (requiring general anaesthesia) in children.
Gastroesophageal reflux disease and *Helicobacter pylori*: Interplay or simply independent?

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**Introduction:** The nature of the relationship between *Helicobacter pylori* (*H. pylori*) and reflux esophagitis is still not clear. To investigate the correlation between *H. pylori* infection and esophagitis taking into account endoscopic and histopathological data.

**Methods:** Between October 2009 and January 2012 a prospective study was performed in 381 patients with gastritis induced by *H. pylori* in order to determine the prevalence of esophagitis and its correlations with the pattern of gastritis and preneoplastic lesions. Finally, univariate analysis of the above mentioned data were performed in order to evaluate the statistical correlation with reflux esophagitis.

**Results:** The prevalence of esophagitis was 9.97%. There were no statistically significant differences between the two groups, with and without esophagitis patients, regarding age and gender, the severity and the pattern of gastritis or the prevalence or the type of the preneoplastic lesions in gastric mucosa.

**Conclusion:** Based on these findings, it seems that there is no significant evidence for an important role for *H. pylori* infection in the development of esophagitis. Nevertheless, current data do not provide sufficient evidence to define the relationship between *H. pylori* and esophagitis. Further assessments in prospective large studies are warranted.
ELSA score – A new tool to evaluate the symptoms in adults with eosinophilic esophagitis

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Aim: It is important to have a tool able to objectively quantify the grade of clinical affection in the follow-up of patients with EoE.

Materials and methods: We have designed a score (Eosinophilic esophagitis Live Symptoms Assessment “ELSA”) which is based on the visual analogic scale model for the 7 most frequent symptoms of adults with EoE: A – Dysphagia, B – Chest pain, C – Cervical knot, D – Regurgitation, E – Pyrosis, F – Epigastralgia, G – Impactations. Each item is graded with a score between 0–10, based on the intensity of the symptom, the week previous to the exam. All the score are summed up and a total score is obtained (0–70 points).

The efficacy of the score was evaluated in 29 patients with EoE pre and post treatment with diets during 6 weeks and comparing the results with 20 healthy subjects.

Results: 29 EoE patients (P) (75% male; mean age 33.29 ± 14.44) with peak eosinophils/cga of 33.86 ± 12.44; were compared with a control group (C) of 20 healthy subjects (60% male; mean age 35.86 ± 12.45). (P vs. C) Total ELSA (30 vs. 3.81; p < 0.00). We compared the post-diet ELSA in responders (n = 20) (R) vs. non-responders (n = 9) (NR): Global ELSA (4.4 vs. 14.67; p < 0.00). In R (preDiet vs. postDiet): A (6.55 vs. 0.85; p < 0.00), B (3.20 vs. 0.35; p < 0.00), C (5.20 vs. 1.05; p < 0.000), D (3.50 vs. 0.45; p = 0.001), E (3.20 vs. 0.60; p < 0.00), F (2.15 vs. 0.25; p = 0.004), G (6.20 vs. 0.85; p < 0.00). In NR a significant descent was only observed in A (6.67 vs. 3.33; p = 0.05)

Conclusion: The ELSA score is an efficient tool in the follow-up of the activity of the EOE because of its ability to quantifying the influence of each of the clinical symptoms of the disease and because of its capacity to improve after the administration of treatment.
Remission of eosinophilic esophagitis with an exclusion diet of less than 4 foods: Is this possible?

J. Rodríguez-Sánchez¹,², E. Gómez Torrijos¹,³, E. De la Santa Belda¹,⁴, F. Martín Dávila¹,⁵, P. PilkingtonWoll¹, J. Olmedo Camacho⁴, P. Reales Figueroa² ¹Multidisciplinary Group of EoE HGUCR/HGOV, ²Gastroenterology Department Hospital Gutiérrez Ortega de Valdepeñas, ³Allergology Department Hospital General Universitario de Ciudad Real, ⁴Gastroenterology Department Hospital General Universitario de Ciudad Real, ⁵Pathology Department Hospital General Universitario de Ciudad Real, Spain

Introduction: It has recently been demonstrated that SFED is effective for the remission of EoE. It is difficult to fulfill, beside to the increased number of endoscopies that the patient has to undergo.

Objective: To analyze the effectiveness of the remission of the EoE (< 15 eo/hpf in the post-diet biopsies) with a selective exclusion diet (SED), elaborated following the sensitization parameters of the allergy tests (SPT [Alk-Abelló] and specific IgE [ImmunoCAP250.PHADIA]) and compare it to the SFED.

Methods: We performed a non-control essay in which patients were included prospectively. Those sensitized to the foods in the allergy tests started SED while those not sensitized started SFED. Non-responders to SED were changed to SFED. Clinical symptoms were monitored using ELSA score.

Results: Thirty-six patients (72.2% males; mean age 34.89 years). We found a mean of 39.25 Eo/hpf in esophageal biopsies during diagnosis. Pre-diet ELSA score of 27.89 points. 21 patients followed SED and 15 SFED. Response to SED vs. SFED: (14/21 (66.7%) vs. 10/15 (66.7%); p = n.s.). SED was elaborated by eliminating a mean of 3.8 foods (1–6), being the most frequent: cereals (44.4%), dried fruit (40%), legumes (39%), diary (30%). 2 of 7 non-responders to SED achieved remission with SFED (28%). We did not find differences in responders to SED vs. SFED in the number of post-diet eo/hpf (1.81 vs. 2.10; p = n.s.), neither in ELSA post-diet (3.19 vs. 1.70; p = n.s.). The rate of global response to diets was of 72.2% (26/36).

Conclusion: SED seems as an efficient strategy in patients sensitized to foods in the allergy tests, with an inferior withdrawal of foods, which means a greater adherence to the treatment. Non-responders to SED presented a sub optimal response to SFED, which could lead to interpreted that the lack of response to SED is a predictor factor of non-response to SFED. Both diets are equivalent in obtaining a remission of clinical symptoms.
Eosinophilic esophagitis: A descriptive study of a series of 35 cases

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**Aim:** The aim of this study was to report our experience with eosinophilic esophagitis patients because there are only few series of cases published in our country.

**Methods:** We retrospectively reviewed the histological data of patients with diagnosis of eosinophilic esophagitis with more than 15 eosinophils per high power field (HPF) in the period 2003–2008 in our hospital.

**Results:** We studied 35 patients; 8 children (3F/5M) and 27 adults (5F/22M), age range mean (6–77 years). The main symptoms in adults were dysphagia in 20 patients (57%) and food impaction in 6 cases (17%) and in children were pyrosis (62.5%) and food impaction (25%). Immunoallergic manifestation appeared in 100% of the studied cases, 97% of them also had peripheral eosinophilia. In 82% of the endoscopies showed pathological findings esophageal rings (40%), whitish exudates (11%), Schatzki ring (11%), foreign bodies (11%) and stenosis esophageal (9%). In 68% of the cases had more than 30 eosinophilic/HPF and only 9% was a range of 15–20 eosinophilic/HPF. The response to treatment during the 4 months follow-up in adults was improvement in 4 patients (15%) treated with oral corticosteroids, 11 patients (41%) with inhaled corticosteroids, 12 patients (37%) with the combination of inhaled corticosteroids and inhibitors of the leucotrien receptor and 2 patients (7%) with periodic esophageal dilatation.

**Discussion/Conclusion:** Our experience says that the incidence is higher in male adult patients with main symptoms dysphagia and food impaction associated with allergic manifestations and esophageal rings in upper endoscopy. With inhaled corticosteroids and inhibitors of the leucotrien receptor and in some cases periodic esophageal dilatation showed good response to treatment.
Quality of life in eosinophilic esophagitis: Validation of the adult eosinophilic esophagitis quality of life (EoE-QoL-A) questionnaire in Spain

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Introduction: The EoE-QoL-A questionnaire was developed in English to evaluate health-related quality of life (HRQoL) in adult eosinophilic esophagitis (EoE) patients; it contains 30 items with 5 impact dimensions of the disease on food/diet, social and emotional impact, anxiety disorder and choking anxiety. To be used in Spanish, its translation, adaptation and validation should be done.

Methods: We developed a multicenter, prospective and observational study: the questionnaire was translated using the translation-retranslation procedure and administered to 100 EoE patients together with others validated questionnaires to evaluate the concurrent validity: the BIPQv2 scale to assess the perception of the disease; the SF12 questionnaire to determine health perception and the HAD scale to evaluate the emotional impact.

Results: For our EoE patients (74.5% male; mean age 30.1), Cronbach’s alpha coefficients showed high values (0.73–0.93) and feasibility excellent (> 99%). The effect on anxiety by disease was the dimension mostly affected, followed by food/diet impact. Non-parametric correlations (Spearman rho) show higher correlation with anxiety than depression (p < 0.01). Relevant and consistent correlations between the perception of the disease and impact of EoE were detected (p < 0.01). Impact of disease, symptoms and discomfort correlated with all dimensions of EoE-QoL-A.

Discussion/Conclusion: The Spanish translation of the EoE-QoL-A determines HRQoL in adult EoE patients and fulfils the psychometric properties required.
Evaluation of eosinophil cationic protein and mast cell tryptase as serum markers for treatment control in eosinophilic esophagitis

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Background: Eosinophilic esophagitis (EoE) is a chronic disease characterized histologically by eosinophilic inflammation with mast cell involvement. Treatment response is usually controlled by esophageal eosinophilic counts requiring consecutive endoscopies with biopsy sampling.

Aim: In order to avoid repeated endoscopies we evaluated the serum markers eosinophil cationic protein (ECP) and mast cell tryptase (MCT) as disease activity marker for treatment control in adults with eosinophilic esophagitis under topical steroid therapy with fluticasone.

Methods: Fifteen patients with eosinophilic esophagitis (EoE) as defined by consensus guidelines completed this prospective study. Before and after three months of therapy with fluticasone 500 µg twice daily eosinophilic and mast cell counts were analyzed quantitatively from histological samples of the esophagus and were correlated with clinical symptoms as well as with serum markers ECP and MCT.

Results: Fluticasone-therapy significantly decreased mean eosinophils (from 42.2 to 16.2 eosinophils/high power field (hpf); p = 0.004) and mast cells (from 13.9 to 5.1 mast cells/hpf; p = 0.001) in the esophageal epithelium. The mean symptoms score also significantly improved (from 34.5 to 19.9 points; p < 0.001). There was a significant decrease of mean ECP (from 15.6 to 5.5 µg/l; p = 0.028) and MCT serum values (from 4.7 to 3.8 µg/l; p = 0.029) under therapy. Serum-ECP correlated significantly with histological eosinophilic counts after fluticasone therapy (r = 0.53; p = 0.038) in contrast to serum MCT.

Conclusions: Histopathological improvement of EoE under topical steroid-therapy with fluticasone is reflected by serum ECP but not by serum MCT levels. Serum ECP appears to be a promising serum marker for treatment control.
Eosinophilic esophagitis in pediatric patients – Histopathological analysis

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Introduction: The most common eosinophilic gastrointestinal disease is eosinophilic esophagitis (EoE), an antigen-driven chronic eosinophil-predominant inflammatory condition that can affect esophageal mucosa at any age in the absence of other potential causes of eosinophilia. Literature reports highlight a rapidly increasing incidence and prevalence rates of pediatric and adult EoE in the past 15 years. The aim of the study was histopathological study of EoE cases diagnosed in the years 2010–2012 in the Department of Medical Pathomorphology, Medical University of Bialystok, based on endoscopic biopsy specimens obtained from the esophagus of children with gastrointestinal disorders, especially with upper aerodigestive symptoms.

Methods: In-depth histopathological assessment of EoE in children aged between 1–18 years used buffered formalin-fixed biopsy specimens collected from the proximal, mid and distal esophagus. The diagnosis of EoE was based on esophageal eosinophilia ≥ 15 eosinophils per high-power field (eos/HPF) in esophageal mucosa.

Results: The retrospective histopathological analysis of biopsy material and clinical observations revealed 31 children (25 boys and 6 girls) diagnosed with EoE. The prevalence of pediatric EoE has shown a growing tendency in the last 2 years. Most cases referred to older children (21 patients), aged 13–18 years. In the study group of 31 patients with EoE, 10 had much higher number of eos/HPF than 15, reaching several tens. Some cases, mainly with much higher eosinophilic count/HPF, showed eosinophil microabscess formation, eosinophil degranulation, basal zone hyperplasia and rete peg elongation. Younger children (aged 1–6 years) usually had feeding aversion, vomiting, documented food allergy and/or regurgitation while in older children (aged 13–18 years) abdominal pain and upper aerodigestive symptoms, mainly dysphagia, were observed.

Discussion/Conclusion: The EoE cases much more frequently involved boys (80.6%), mostly those aged 13–18 years, who presented with abdominal pain and upper aerodigestive symptoms, especially when histopathological lesions were intense.
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Abstracts
Poster Abstracts

Eosinophilic Esophagitis: A Novel Chronic-Inflammatory Disease of the GI Tract

September 6 – 7, 2013
Messe Congress Graz
Graz, Austria

Innovative Drugs
for bowel and liver diseases
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Scientific Dialogue
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