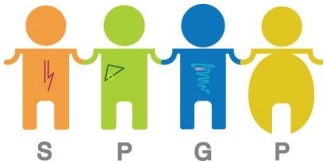


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Hot Topics
em
Gastroenterologia Pediátrica

Eosinófilos e Tubo Digestivo

Ricardo Ferreira

Gastroenterologia e Nutrição Pediátrica

Hospital Pediátrico de Coimbra

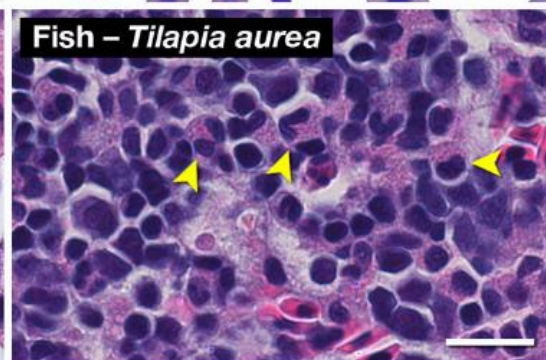
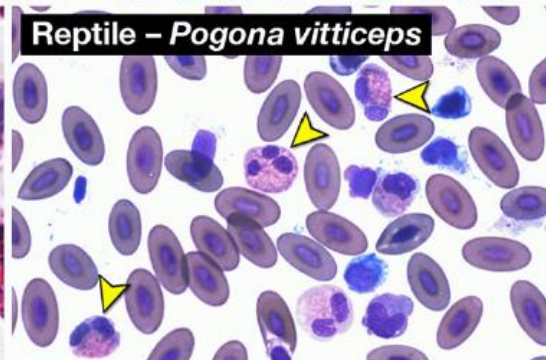
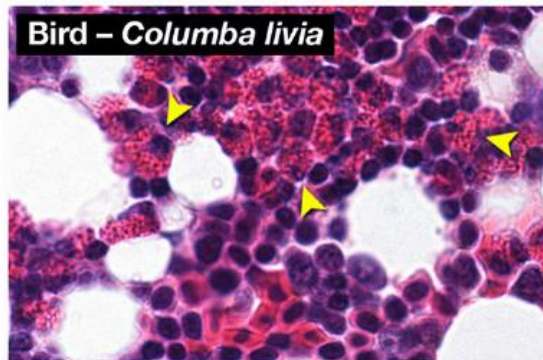
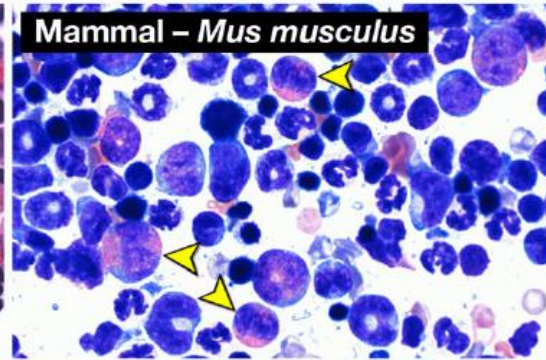
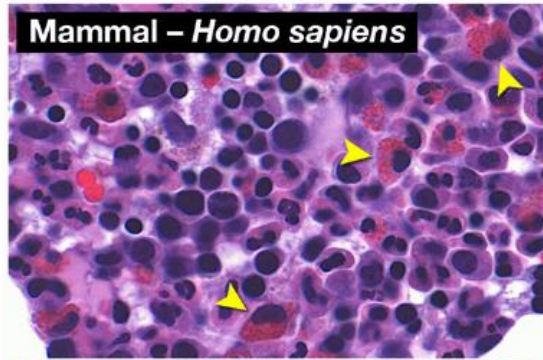
Eosinófilos – para que servem?

- **1880–1960** **Paul Erlich to the Mid-20th Century**
Eosinophils are mediators of host defense and causative agents of allergic symptoms and pathologies
- **1960–1980** **The Early Anti-inflammatory Years**
Eosinophils are recruited to inflamed tissues to dampen the activities mediated by resident pro-inflammatory tissue leukocytes
- **1980–2000** **The “Gleich Era”**
The rebirth of the non-specific and destructive end-stage effector cell hypothesis contributing to both disease symptoms and pathologies
- **2000–present** **The **LIAR** Hypothesis**
*Eosinophils are critical components of mechanisms necessary for tissue homeostasis through **Local Immune And Remodeling / Repair** activities*

Eosinófilos em todos vertebrados

Lee et al.

Page 17



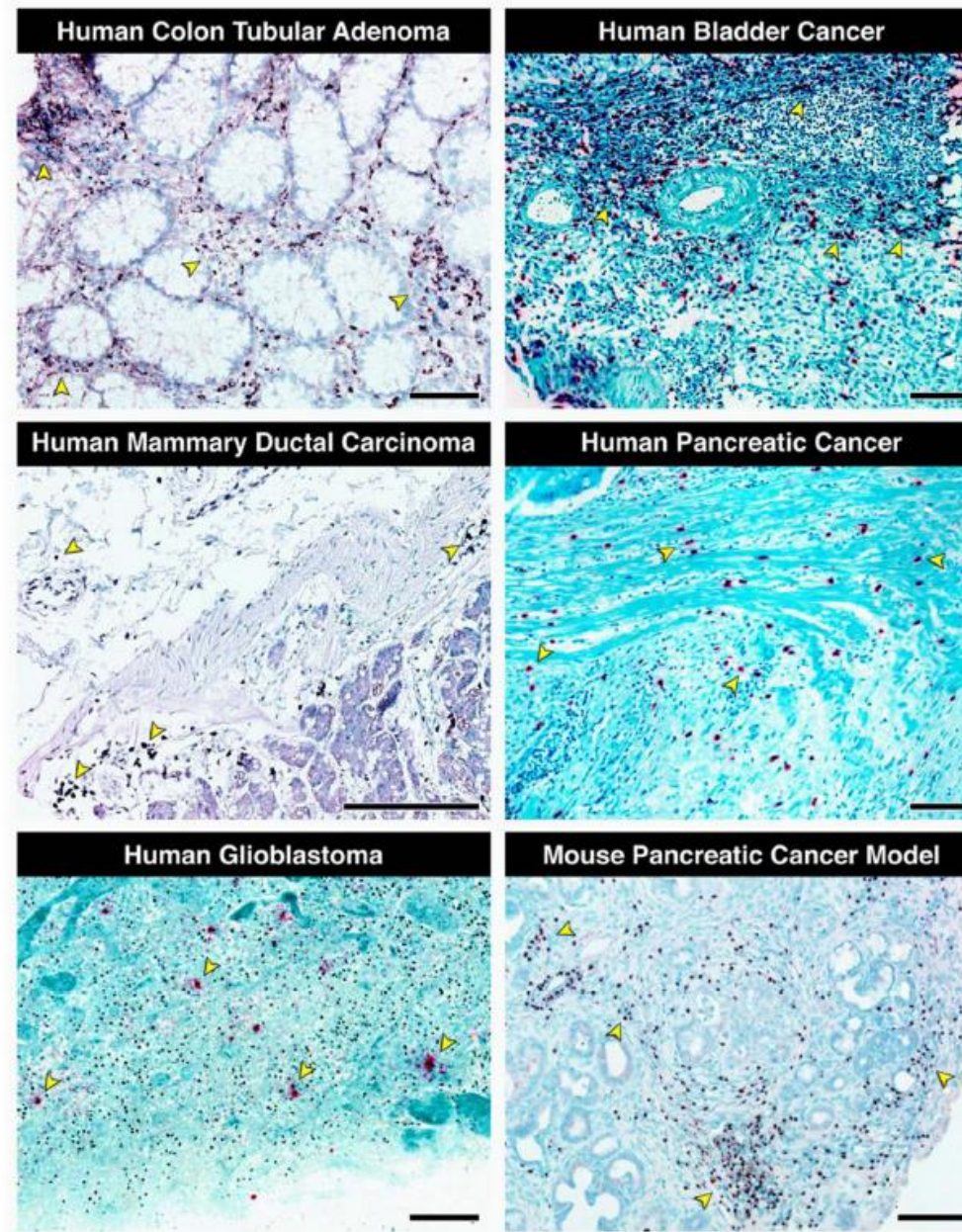


Figure 4. Histopathological assessments of biopsies from human cancers and tumors from mouse models of cancer show that eosinophil infiltration of tumors is often significant and, more importantly, a widely occurring phenomenon

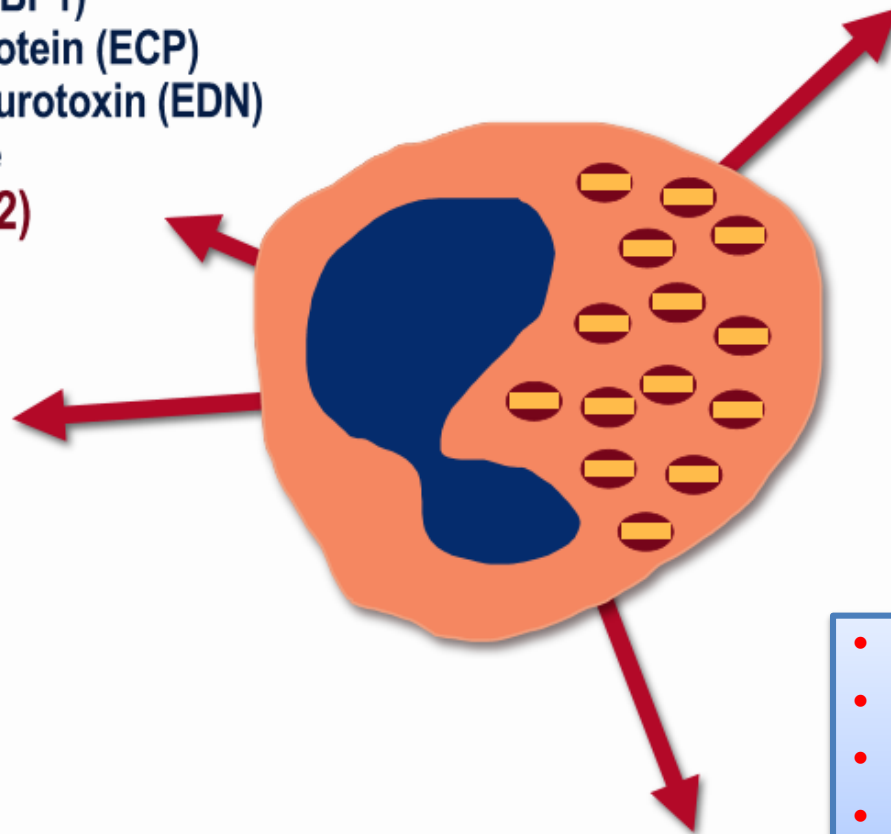
Secretory Products of Eosinophils

Granule-derived proteins

Major basic protein (MBP1)
Eosinophil cationic protein (ECP)
Eosinophil-derived neurotoxin (EDN)
Eosinophil peroxidase
MBP homolog(MBP2)

Reactive oxygen intermediates

Oxygen and peroxide
Hydroxyl radicals
Singlet oxygen



Lipid mediators

Leukotriene C4/D4
Platelet activating factor
5-HETE
5,15- and 8,15-diHETE
Prostaglandin E₁ E₂
Thromboxane B₂

Cytokines

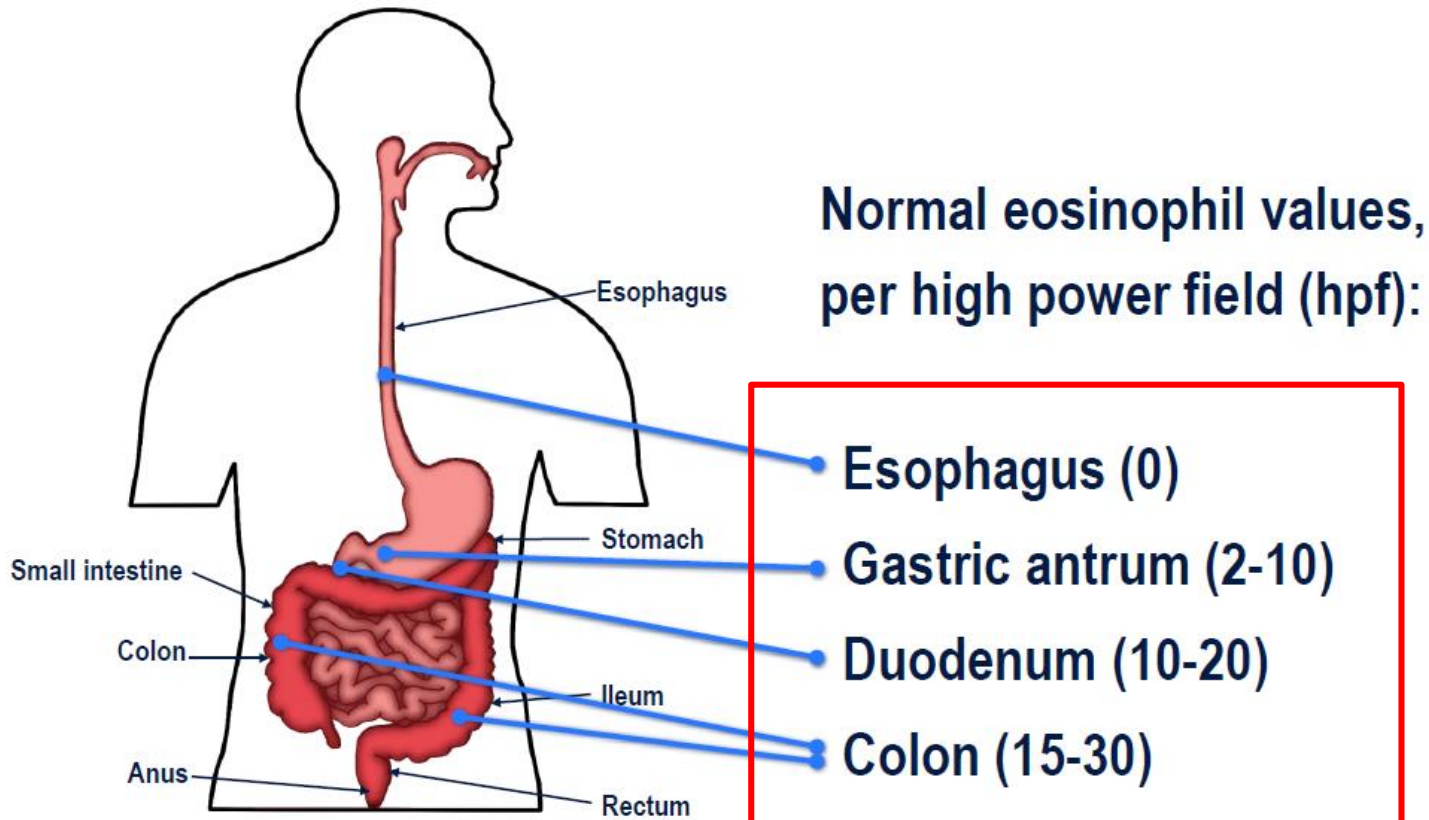
- **Eotaxin-3**
- **IL-5**
- **IL-13**
- **TGF-beta**
- **pSMAD**

Síndromes hipereosinofílicas

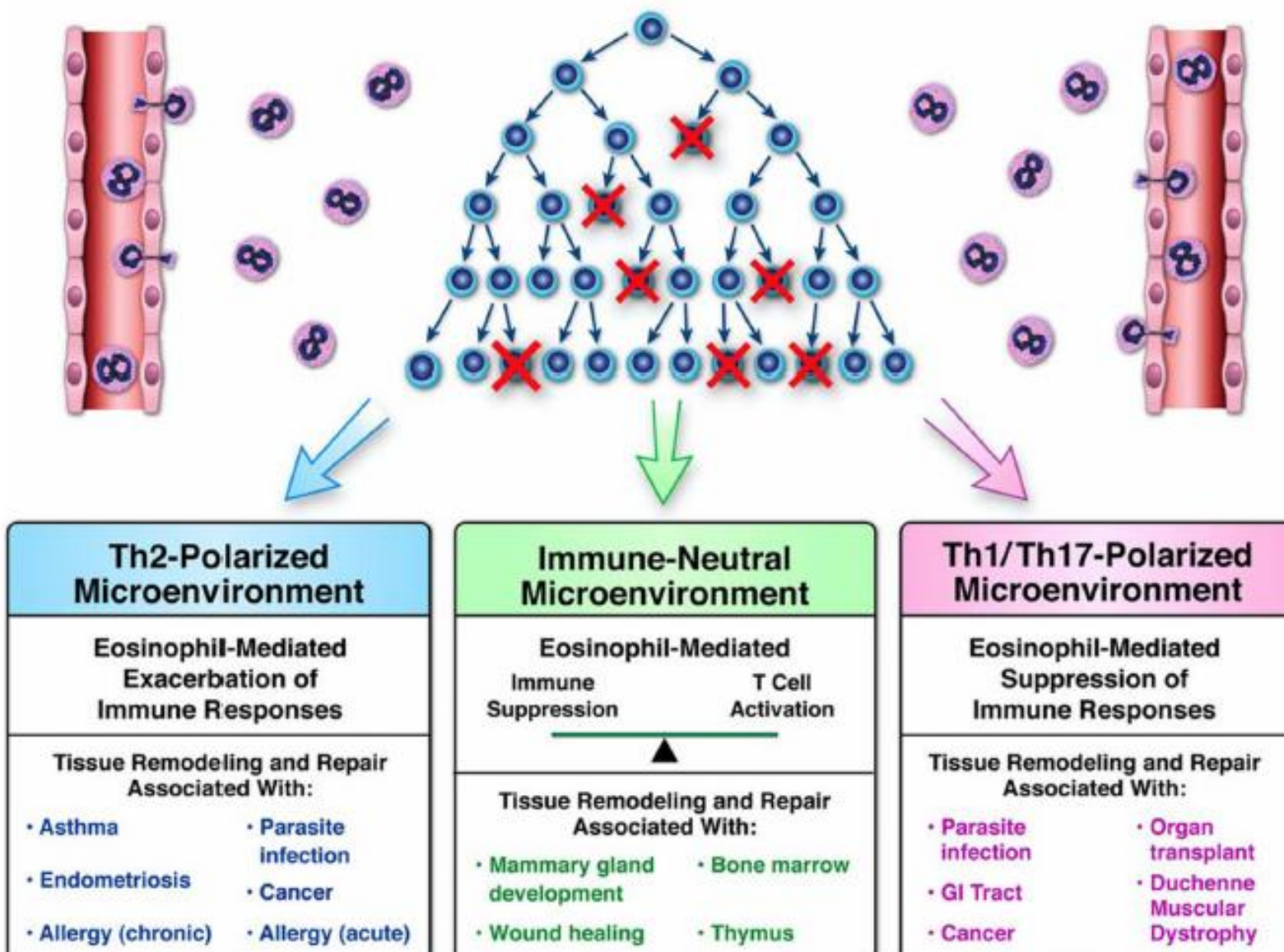
- Entidade rara / mieloproliferativa
- $> 1500 \text{ Eos/mm}^3$ (30-70% leucócitos)
- Lesão em órgãos – alvo
 - Pele
 - Coração
 - Sistema Nervoso
 - Fígado
 - Pulmão, ...

O que fazem no tubo digestivo?

Gastrointestinal Eosinophils

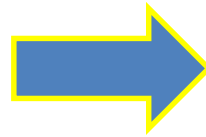


Average accepted values

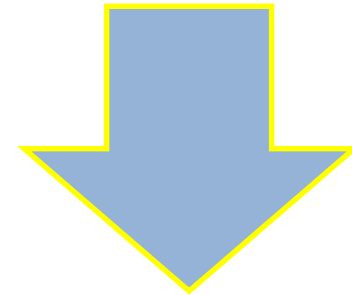
Eosinophils in Health and Disease: The LIAR Hypothesis

Infiltração eosinofílica do tubo digestivo

- **Esofagite Eosinofílica**
- **Gastroenterite Eosinofílica**
- **Colite Eosinofílica, ...**



**Doenças
Gastrointestinais
Eosinofílicas
(EGIDs)**

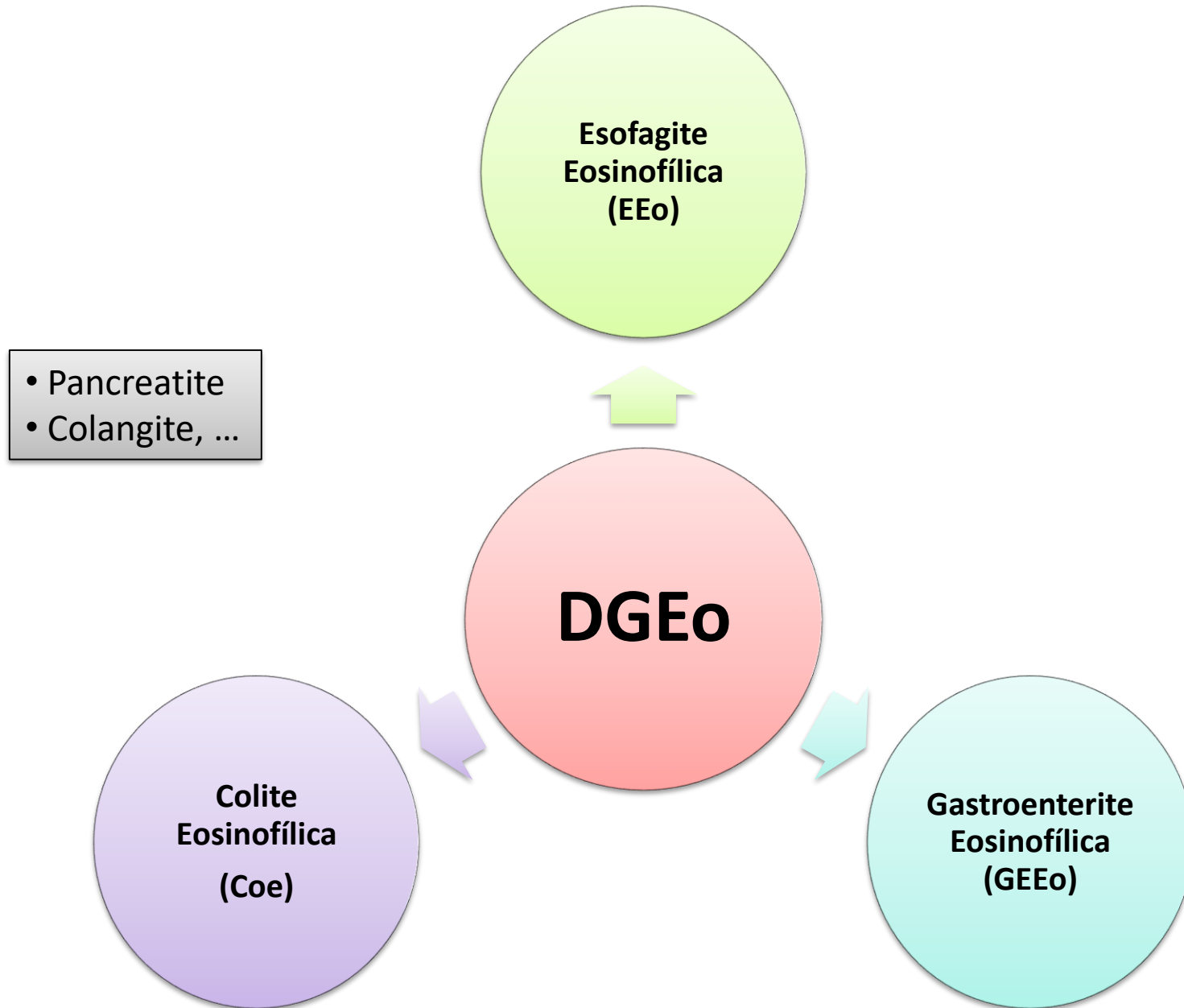


Eosinofilia secundária

- Esofagite de Refluxo
- Alergia Alimentar (IgE)
- Infecções por Parasitas
- D. Celíaca
- D. Infl. Intestinal (D. Crohn)
- Rejeição de transplante
- D. tecido conjuntivo
- Fármacos

- **Sem relação com hipereosinofilia sanguínea
(≠ Sind. Hipereosinofílicos)**
- **A alergia é uma suspeita frequente...**

D. Gastrointestinais Eosinofílicas (DGEo)



Prevalence of Eosinophilic Gastritis, Gastroenteritis, and Colitis: Estimates From a National Administrative Database

*Elizabeth T. Jensen, [†]Christopher F. Martin, [‡]Michael D. Kappelman, and *Evan S. Dellon

See “Eosinophilic Gastrointestinal Disorders Affect More Than Just the Esophagus” by Furuta et al on page 1.

ABSTRACT

Objectives: Eosinophilic esophagitis (EoE) is becoming increasingly more common, but the prevalence of other eosinophilic gastrointestinal disorders (EGIDs) is unknown. Our objective was to estimate the prevalence of eosinophilic gastritis, gastroenteritis, and colitis in the United States.

Methods: We used the IMS Health LifeLink PharMetrics Plus Claims Database, data representative of a US national commercially insured population containing medical and pharmaceutical claims for >75 million individuals. We restricted our sample to patients ages 0 to 64 with continuous enrollment between July 1, 2009, and June 30, 2011. We identified patients with eosinophilic gastritis, gastroenteritis, and colitis as defined by ≥ 1 instance of the *International Classification of Diseases, Ninth Revision* codes 535.70, 558.41, and 558.42, respectively. We calculated the prevalence of the codes in the database and then standardized the estimates to the US population by age and sex.

What Is Known

- The prevalence of noneosinophilic esophagitis eosinophilic gastrointestinal disorders is poorly described in the literature.
- The introduction of the *International Classification of Diseases, Ninth Revision* codes for these conditions provided the opportunity to estimate the prevalence of these conditions in the United States.

What Is New

- Eosinophilic gastritis, gastroenteritis, and colitis are rare, with a standardized prevalence of 6.3/100,000, 8.4/100,000, and 3.3/100,000, respectively.
- The prevalence of eosinophilic gastroenteritis was the highest among children age <5 years, whereas eosinophilic gastritis was more prevalent among older age groups. We observed no age differences for eosinophilic colitis.

JPGN • Volume 62, Number 1, January 2016

Prevalence of Eosinophilic Gastrointestinal Disorders

TABLE 3. Prevalence of eosinophilic GI diseases by age, sex, and region

	Source population (n)	Eosinophilic gastritis		Eosinophilic gastroenteritis		Eosinophilic colitis	
		Patients (n)	Prevalence (per 100,000)	Patients (n)	Prevalence (per 100,000)	Patients (n)	Prevalence (per 100,000)
Age, y [*]							
<20	3,587,571	159	4.4	385	10.7	153	4.3
20–64	7,981,646	615	7.7	569	7.1	251	3.1
Sex							
Male	5,544,574	299	5.4	423	7.6	173	3.1
Female	6,024,643	475	7.9	531	8.8	231	3.8

D. Gastrointestinais Eosinofílicas

- Reconhecimento recente e crescente
- Clínica é inespecífica (excepto EEO) e vai depender:
- **1 – Segmento afectado**
 - Esófago apenas: Esofagite Eosinofílica (EEO)
 - Tubo digestivo alto: Gastrite / Gastroenterite Eosinofílica
 - Colon: Colite Eosinofílica
- **2 - Intensidade e profundidade da infiltração eosinofílica**
- **3 - Resposta dos tecidos à inflamação**

Clínica: segmento / resposta inflam.

- **Esófago:** - disfagia, impacto alimentar, vômitos, RGE-like
- **Estômago:** - vômitos, epigastralgias, atraso esvaziamento gástrico
- **Intest. delgado:** - diarreia, distensão abdominal, dor abdominal,
- enteropatia perdedora de proteínas, anemia crônica
- **Colon:** - diarreia com muco / sangue, urgência em defecar

- **Apenas alt. da mucosa:** - ulceração, hemorragia, má absorção, ...
- **Infiltração da camada muscular:** - sintomas obstrutivos, alt. motilidade
- **Infiltração da sub-serosa e serosa:** - ascite rica em Eosin., “plastron-like”

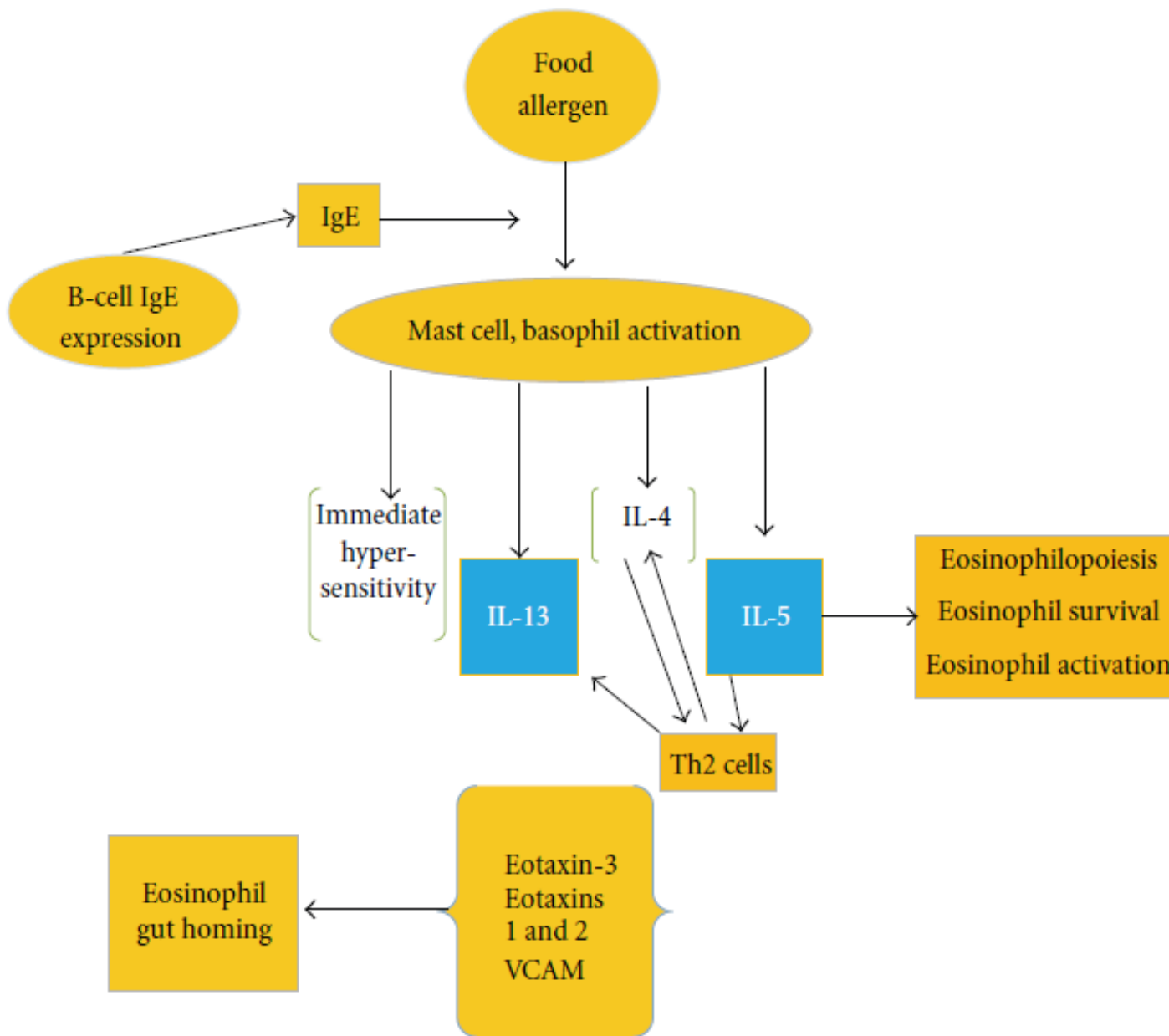


FIGURE 1: Pathophysiology in EGID.

Relação com Alergia

- A alergia é frequentemente suspeitada, mas por vezes é difícil de provar
- Mais associada com a EEO (40-60%) do que nas restantes entidades
- Fisiopatologia intermédia entre IgE-mediada e hipersensibilidade retardada
- Alimentos + envolvidos:
 - Leite de vaca
 - Ovo
 - Peixe
 - Cereais, Frutos secos, Marisco
- Na EEO a resposta à dieta elementar é boa
- **Nas outras entidades, a resposta às dietas de eliminação é pior do que a resposta aos corticoides (tópicos, sistémicos)**

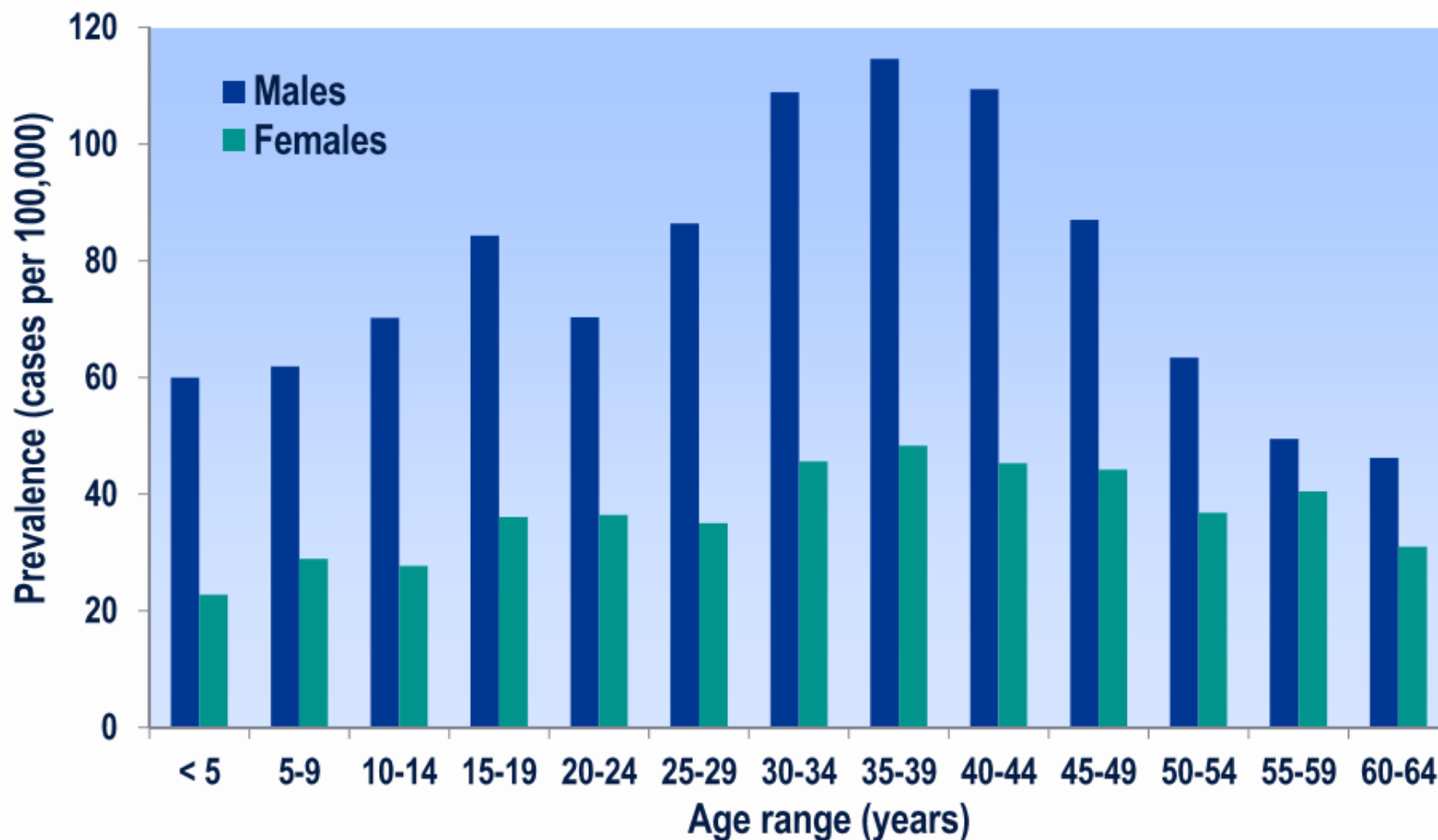
Management Guidelines of Eosinophilic Esophagitis in Childhood

A. Papadopoulou, [†]S. Koletzko, [‡]R. Heuschkel, [§]J.A. Dias, ^{||}K.J. Allen, [¶]S.H. Murch, [#]S. Chong, ^{}F. Gottrand, ^{††}S. Husby, ^{‡‡}P. Lionetti, ^{§§}M.L. Mearin, ^{||||}F.M. Ruemmele, ^{¶¶}M.G. Schäppi, ^{##}A. Staiano, ^{***}M. Wilschanski, and ^{†††}Y. Vandenplas, for the ESPGHAN Eosinophilic Esophagitis Working Group and the Gastroenterology Committee*

RECOMMENDATION

In symptomatic children with histological findings of esophageal eosinophilia, a trial of PPIs is recommended for 8 weeks. A second EGD should be performed under PPI therapy in all children, even if symptoms resolve (Fig. 1). If histology is still suggestive of EoE and other causes of esophageal eosinophilia are unlikely, then the diagnosis of EoE can be made. If the first endoscopy is performed after the patient has already had an adequate trial of PPI, the diagnosis of EoE can also be made and specific treatment for EoE be initiated.

Prevalence of EoE by Age & Sex



Dellon et al. *Clin Gastroenterol Hepatol*. 2013; S1542-3565(13)01304-9.

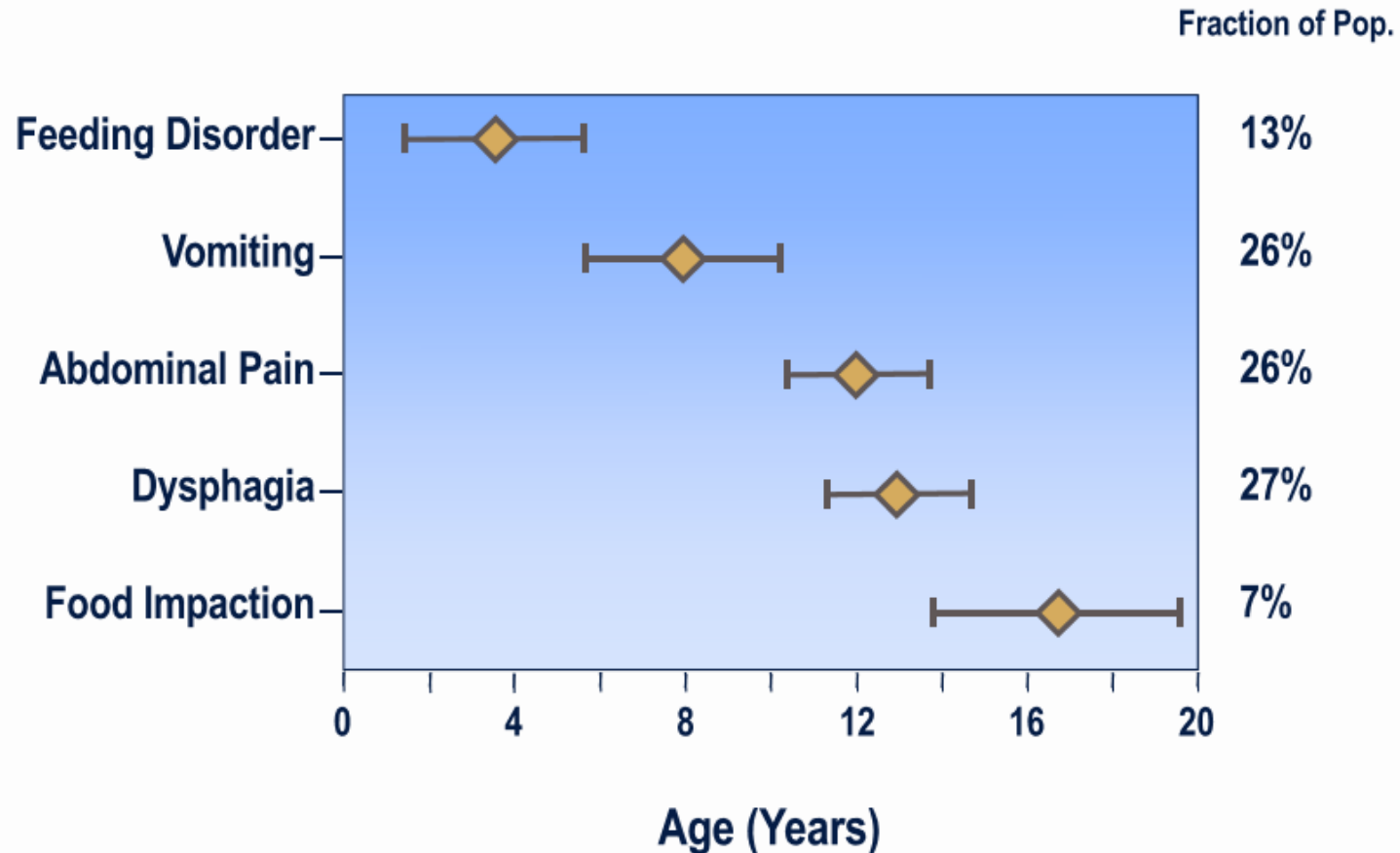


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EoE Presentation by Age



Noel et al. *N Engl J Med.* 2004; 351:940-941.



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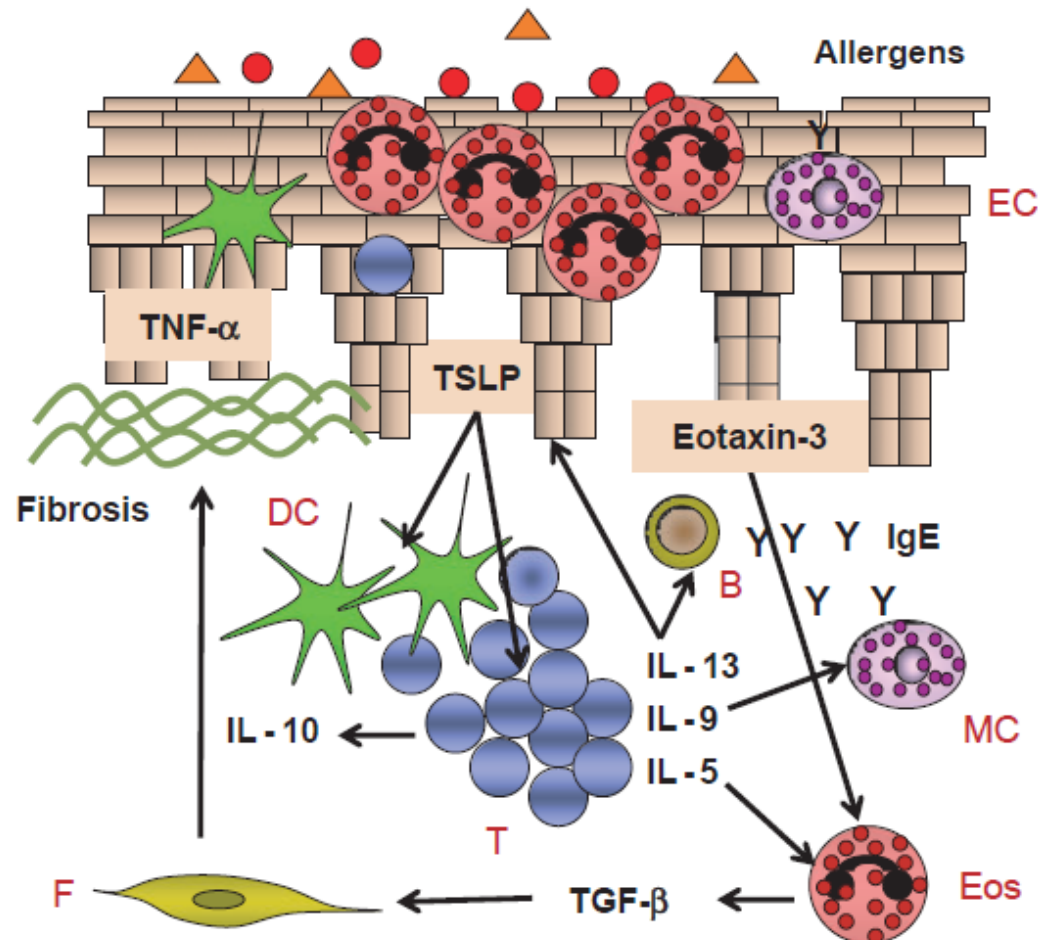
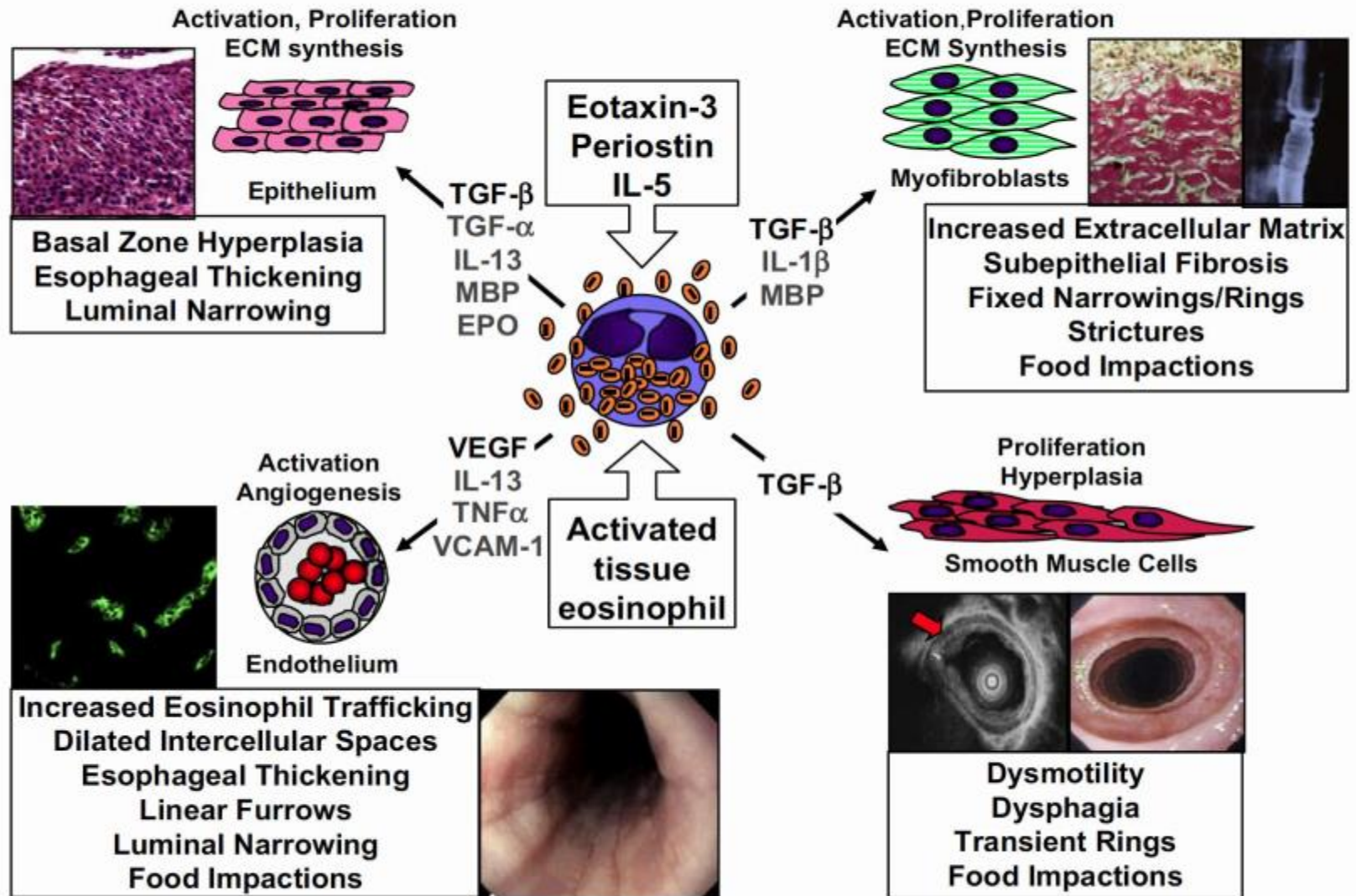


Figure 3 Simplified scheme on the immunopathogenesis of eosinophilic esophagitis (EoE). EoE is believed to be triggered by aero- and food allergens. The epithelial cells (EC) of the esophagus that are activated by IL-13 actively contribute to the inflammatory process. Thymic stromal lymphopoietin promotes dendritic cell (DC)-mediated Th2 differentiation, TNF- α increases adhesion molecules on endothelial cells (not shown), and eotaxin-3 attracts eosinophils (Eos). IL-13 helps B cells to produce IgE. IL-9 activates mast cells (MC), which bind IgE by their high-affinity IgE receptor. IL-5 activates eosinophils and may delay their apoptosis. There are also

IL-10-generating T cells, which likely try to limit the inflammatory process. Eos and MC generate additional cytokines and participate in the immunoregulatory process (not shown). Eos also generates TGF- β , which stimulates fibroblasts (F) to produce extracellular matrix proteins. Eos may also damage epithelial cells by releasing cationic proteins and reactive oxygen species (not shown). It should be noted that mast cells and eosinophils generate additional inflammatory mediators that help in recruiting leukocytes (not shown), which subsequently migrate in the epithelial layer of the esophagus.

Molecular Microenvironment in EoE



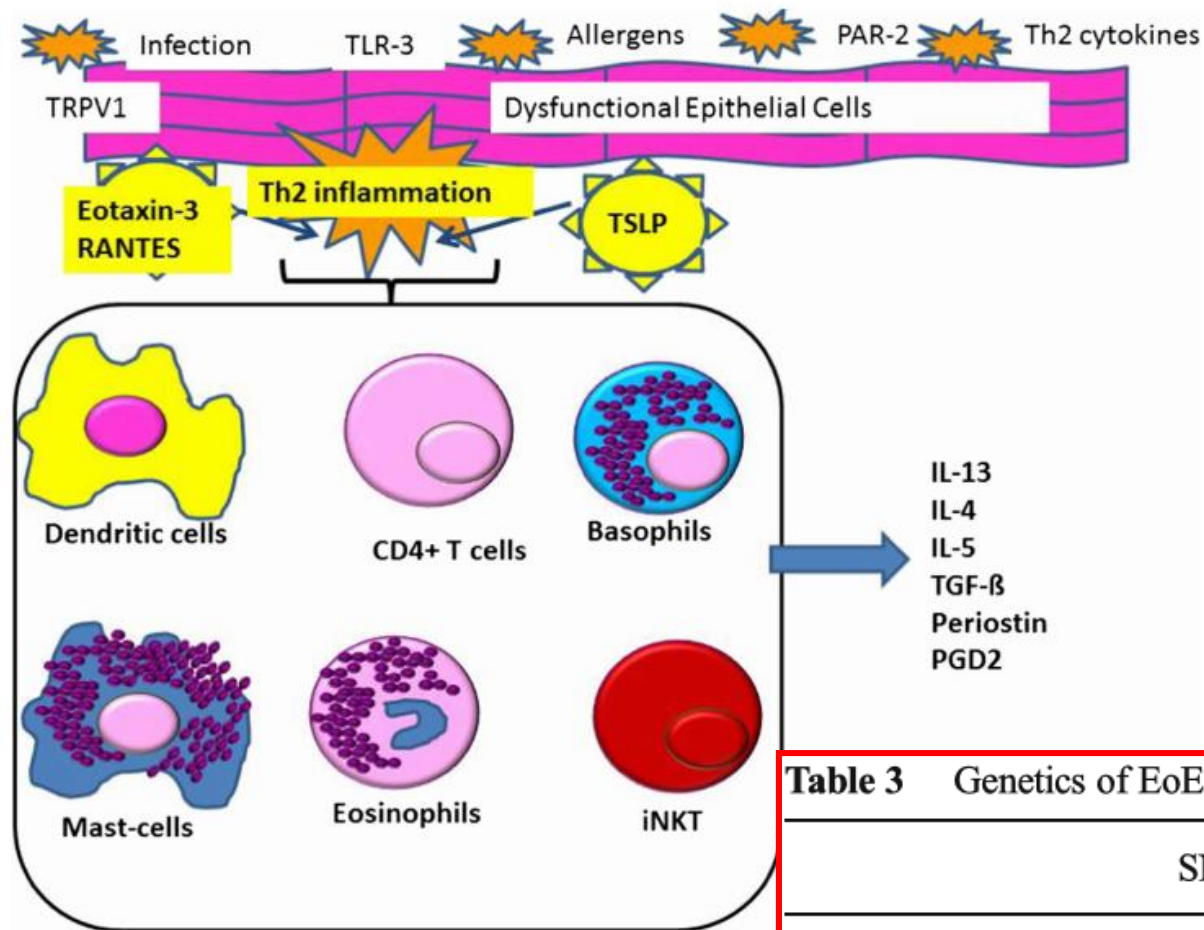


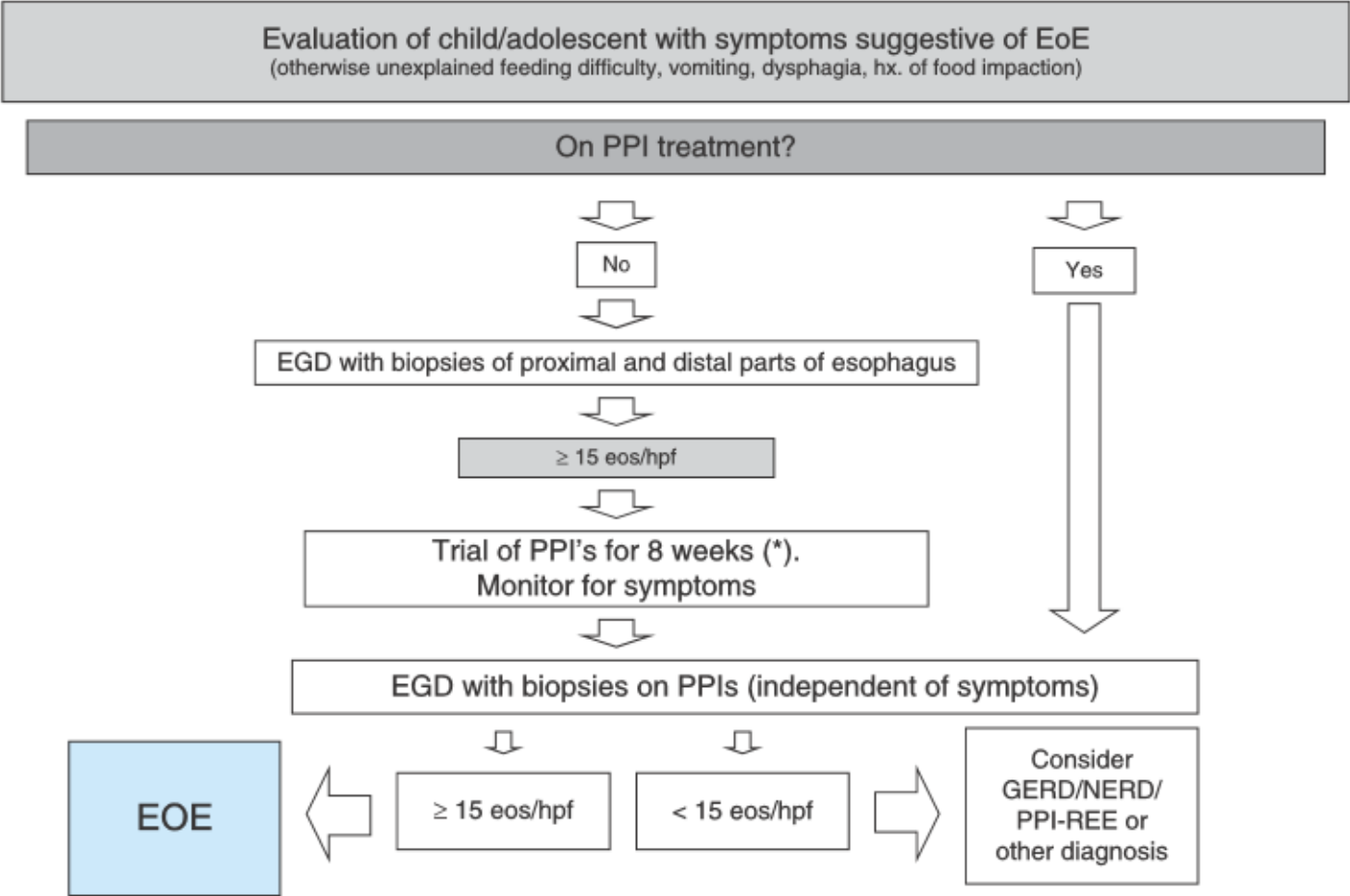
Table 3 Genetics of EoE

	SNP	Chromosome
TSLP SNP	rs3806932 (A/G)	5q.22.1
TSLP-R SNP	rs36133495 (A/V)	Xp22.3; Yp11.3
Eotaxin 3	rs2302009 (T/G)	7q11.23
CAPN14	rs77569859 (G/A)	2q.23
EMSY	rs55646091	11q13.5

Eosinophilic Esophagitis: A Comprehensive Review

Antonella Cianferoni^{1,2} • Jonathan Spergel^{1,2}

Clinic Rev Allerg Immunol



Alterações endoscópicas

- **Esofagite Eosinofílica – aspecto endoscópico “típico”**

- Estrias longitudinais
- Aneis (traquealização)
- Pápulas esbranquiçadas, estenose

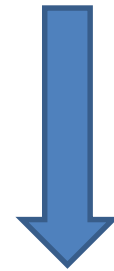
- **Gastrite Eosinofílica**

- Pseudo-pólipos, nódulos esbranquiçados
- Obstrução pré-pilórica ou pilórica

- **Colite Eosinofílica**

- Perda do padrão vascular
- Eritema
- Hiperplasia nodular

**O aspecto
endoscópico
pode ser Normal!**



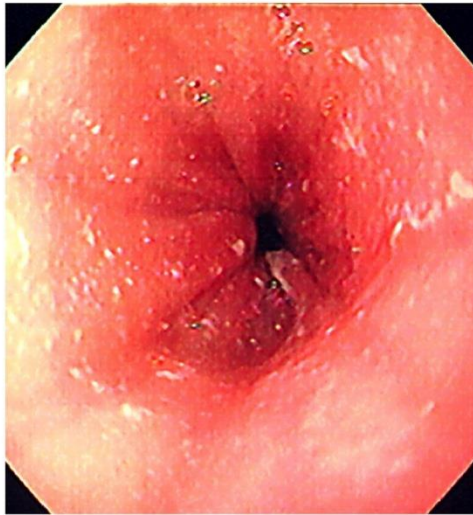
**Biópsias
múltiplas!**

Esofagite Eosinofílica

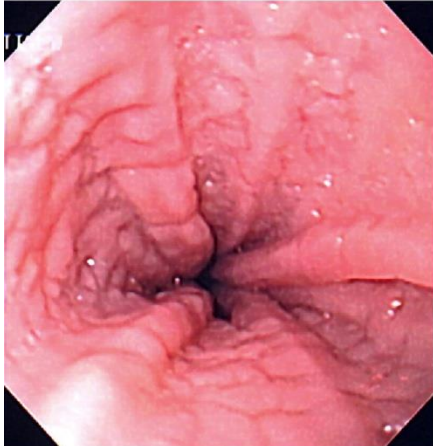
A



B



A



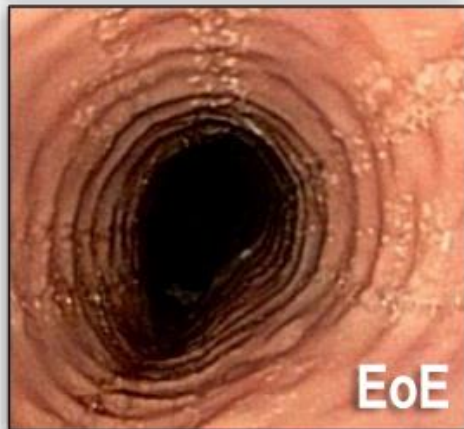
B



C



Classification/Grading System for Endoscopically Detected Esophageal Features of EoE -EREFS



- E**dema (pallor)
- R**ings (“trachealization”)
- E**xudates (plaques)
- F**urrows (vertical lines)
- S**tricture
 - Mucosal fragility
 - Narrow caliber esophagus

Histopatologia

- Diagnóstico + fácil no esófago (habitualmente não há eosinófilos!)
(0-7 Eo /CGA:  RGE; > 15 Eo:  EEO)
- O cólon direito tem bastantes eosinófilos (> 30-40 Eo)
- O cólon distal tem poucos eosinófilos...
- **A contagem de eosinófilos é fundamental, mas não é o único dado!**
 - Grau de desgranulação dos eosinófilos
 - Permeação das várias camadas da mucosa
 - Formação de agregados / micro-abcessos
 - Identificação de citocinas dos eosinófilos

Sem alteração da arquitectura da mucosa!

(≠ D. Inflamatória Intestinal)

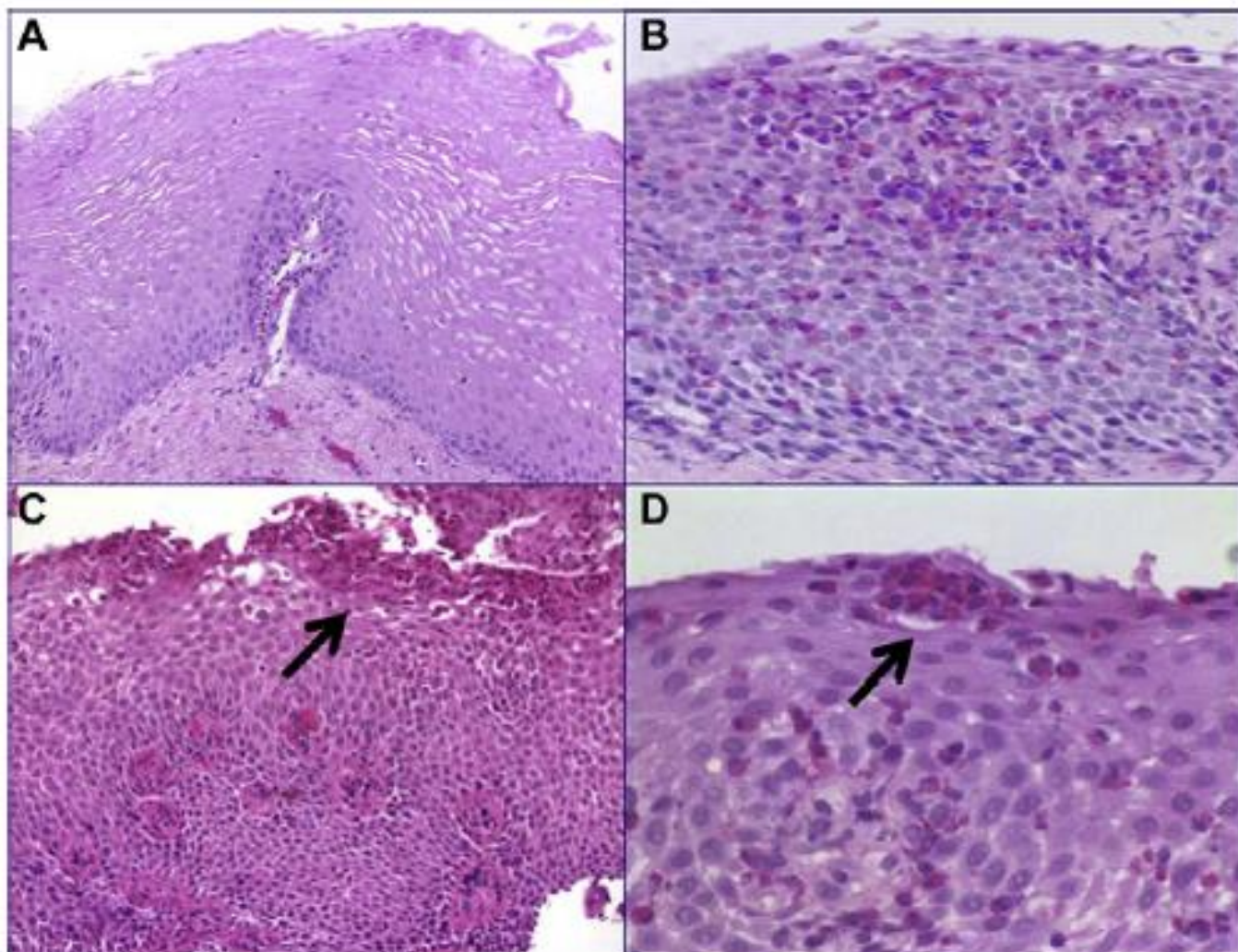
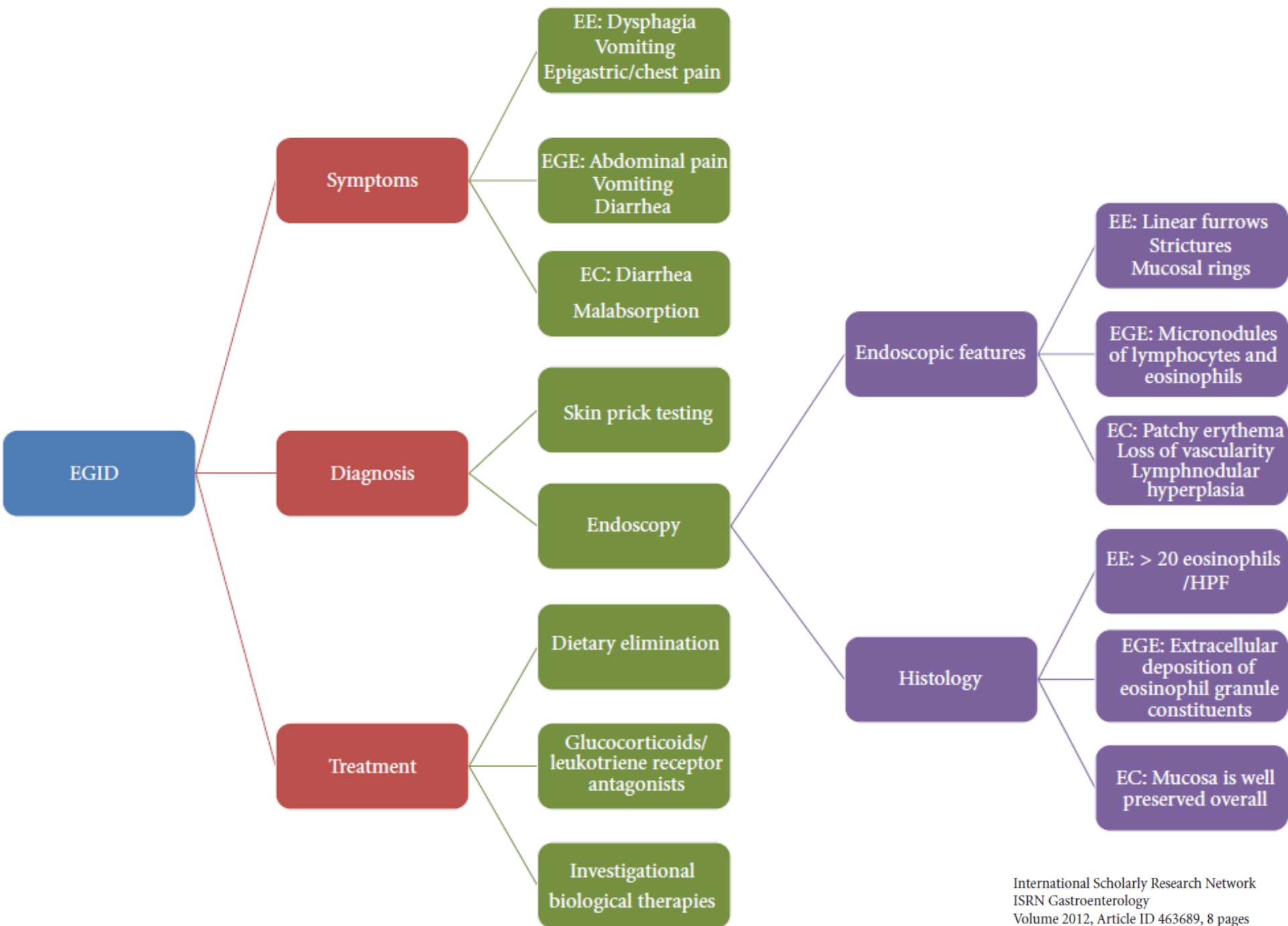
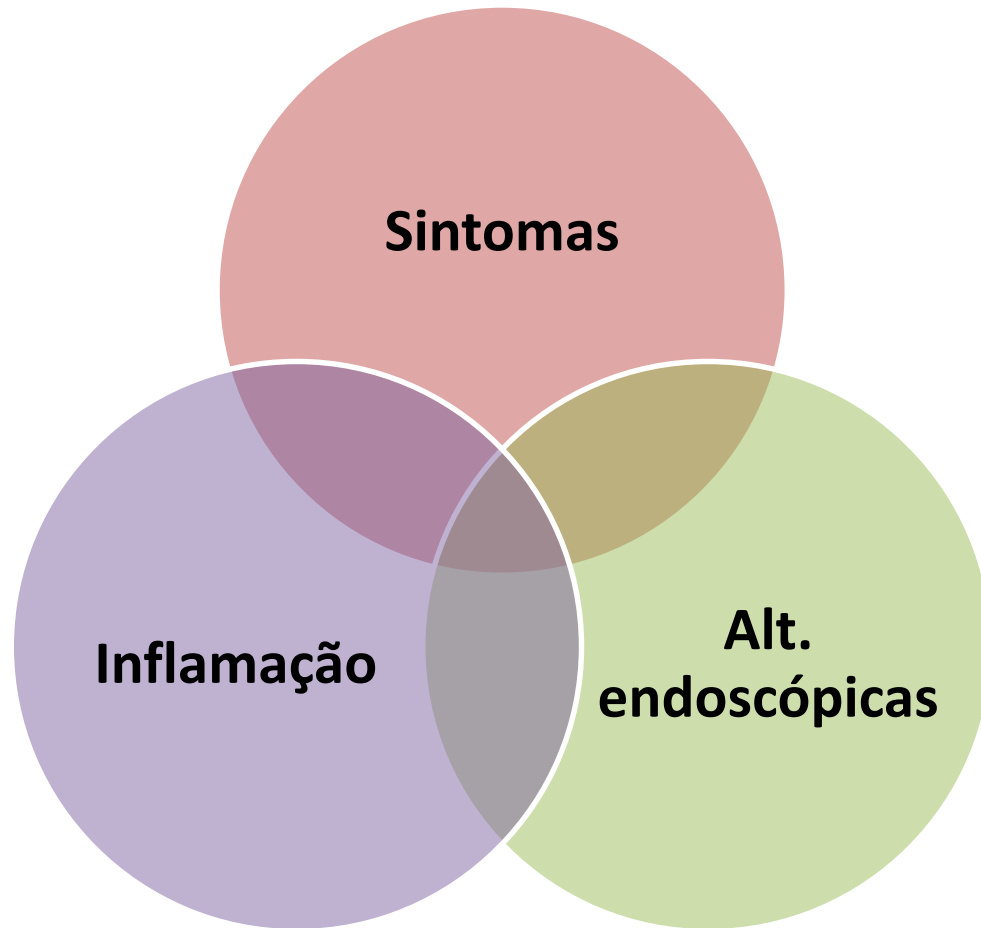


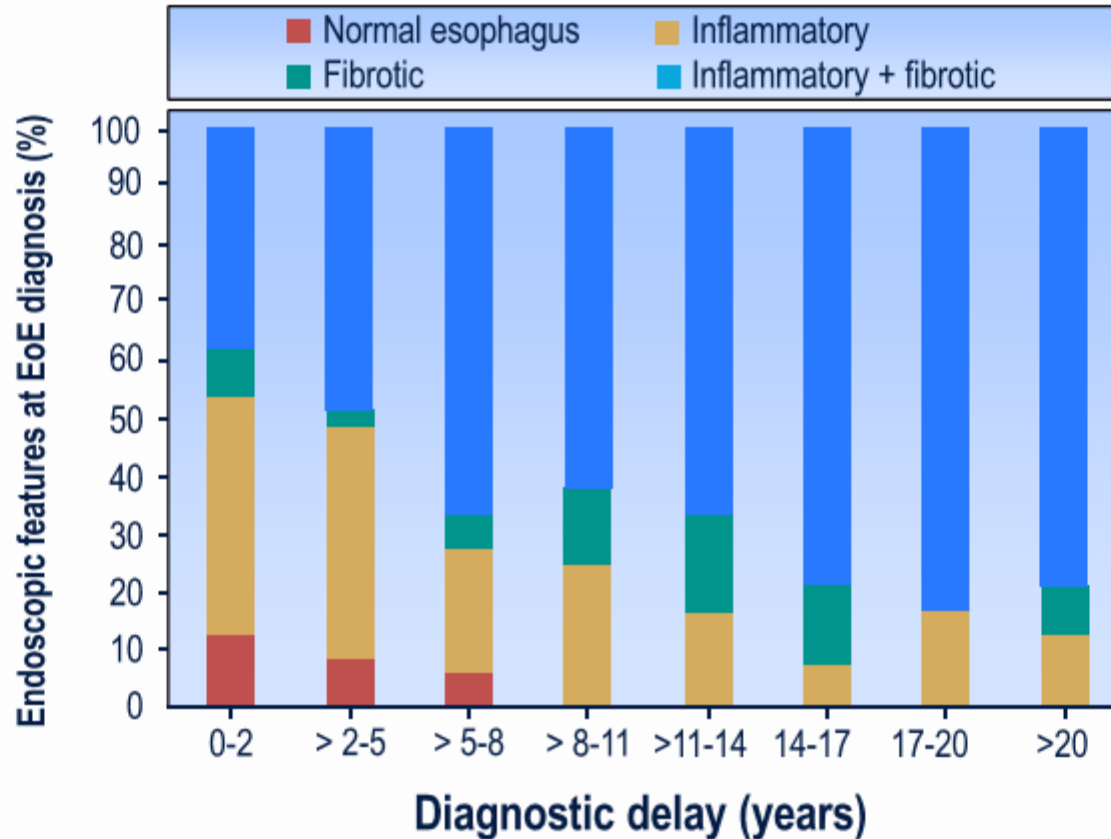
FIG 1. Histology of the esophagus (mucosal biopsy specimens). **A**, Normal esophagus. **B**, EoE. **C**, EoE, superficial layering of surface eosinophils (*arrow*). **D**, EoE, microabscess (*arrow*).



EEo - Objetivos da terapêutica



Natural History – Adult Study



EEO - Terapêutica e vigilância

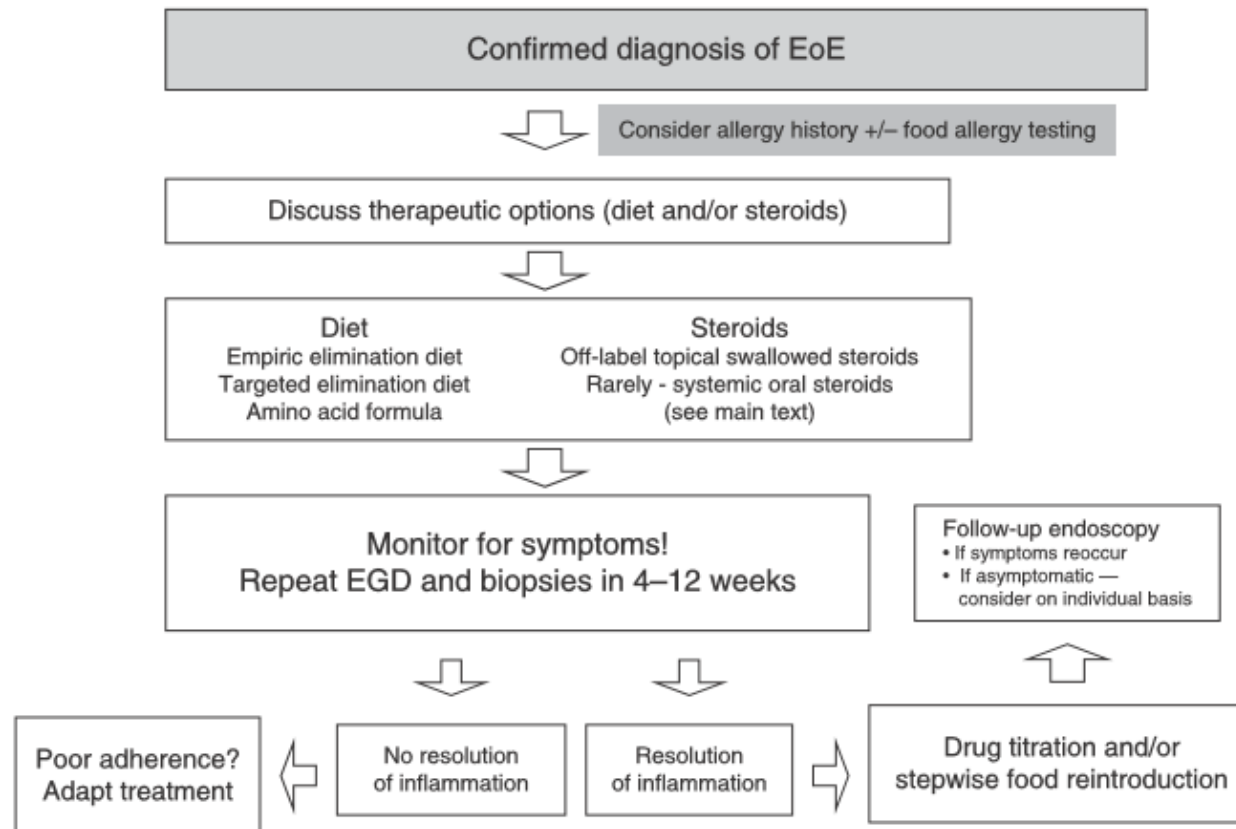


FIGURE 2. Algorithm for the management of children and adolescents with eosinophilic esophagitis (EoE). EGD = esophagogastroduodenoscopy.

EEo - terapêutica

Dieta

- Dieta elementar
- Dieta de exclusão selectiva, orientada (clínica, testes alergol.)
- Dieta dos 6 alimentos (SFED)

Corticoide tópico

- Fluticasona
- Budesonido

Corticoide sistémico

Dilatação esofágica

Terapêutica “biológica”

Dieta Elementar – resultados na EEO

Table 1 Summary of studies of elemental formula

Reference	n	Population	Design	Mean age, years	Clinical response	Histologic response	Residual eosinophil count
Kelly et al ¹⁷	10	Children	Prospective	4.8 (8 months to 12.5 years)	10/10 (100%)	<20 eos/hpf: 9/10 (90%)	41 → 0.5 (<i>P</i> =0.005)
Markowitz et al ¹⁸	51	Children	Retrospective	8.3±3.1	49/51 (96%)	<20 eos/hpf: 49/51 (96%)	33.7 → 1.0 (<i>P</i> <0.01)
Liacouras et al ¹⁹	172	Children	Retrospective	8.1±4.3	160/164 (98%)	<20 eos/hpf: 160/164 (98%)	38.7 → 1.1 (<i>P</i> <0.001)
Kagalwalla et al ²⁰	25	Children	Retrospective	6.4	25/25 (100%)	≤10 eos/hpf: 22/25 (88%)	58.8 → 3.7 (<i>P</i> <0.001)
Peterson et al ²⁵	18	Adults	Prospective	34±12	No clinical improvement	≤10 eos/hpf: 13/18 (72%)	54 → 10 (<i>P</i> =0.0006)
Henderson et al ²²	49	Children	Retrospective	5.6	Not available	<15 eos/hpf: 47/49 (96%)	51.0 → 1.0 (<i>P</i> <0.0001)

Abbreviation: eos/hpf, eosinophils per high-powered field.

EEo - dieta

- **A dieta elementar**
- Dieta de exclusão dirigida (TED – ***Targeted Elimination Diet***)
- Dieta de exclusão empírica (dieta dos 6 alimentos – ***SFED – Six Food Elimination Diet***)
 - Leite e derivados
 - Soja
 - Trigo
 - Amendoim
 - Marisco / peixe
- Duração de 4-12 semanas (pelo menos 6-8 semanas)
- Melhora a inflamação, mas pode não alterar a sintomatologia (ex: estenose)
- **A dieta elementar (AA livres) mostrou ser a mais eficaz**, mas é de aplicação difícil
- **Controlo da eficácia (Clínica, EDA de controlo)**

Least allergenic

Most allergenic

(Add several foods
over a period of time)

(Add one food over
a period of time)

A	B	C	D
Vegetables (non-legume) Carrots, squash (all types, sweet potato, white potato, string beans, broccoli, lettuce, beets, asparagus, cauliflower, brussel sprouts Fruit (non-citrus, non-tropical) Apple, pear, peaches, plum, apricot, nectarine, grape, raisins Vegetables Tomatoes, celery, cucumber, onion, garlic, any other vegetables	Citrus fruits Orange, grapefruit, lemon, lime Tropical fruits Banana, kiwi, pineapple, mango, papaya, guava, avocado Melons Honeydew, cantaloupe, watermelon Berries Strawberry, blueberry, raspberry, cherry, cranberry Grains Rice, millet, quinoa	Legumes Lima beans, chickpeas, white/black/red beans Grains Oat, barley, rye, other grains Meat* Lamb, chicken, turkey, pork *Progress from well-cooked to rarer	Fish/shellfish Corn Peas Peanut Wheat Beef Soy Egg Milk

Figure 4. Dietary reintroduction of food allergens. Modified with permission from Spergel and Shuker.¹⁵⁴

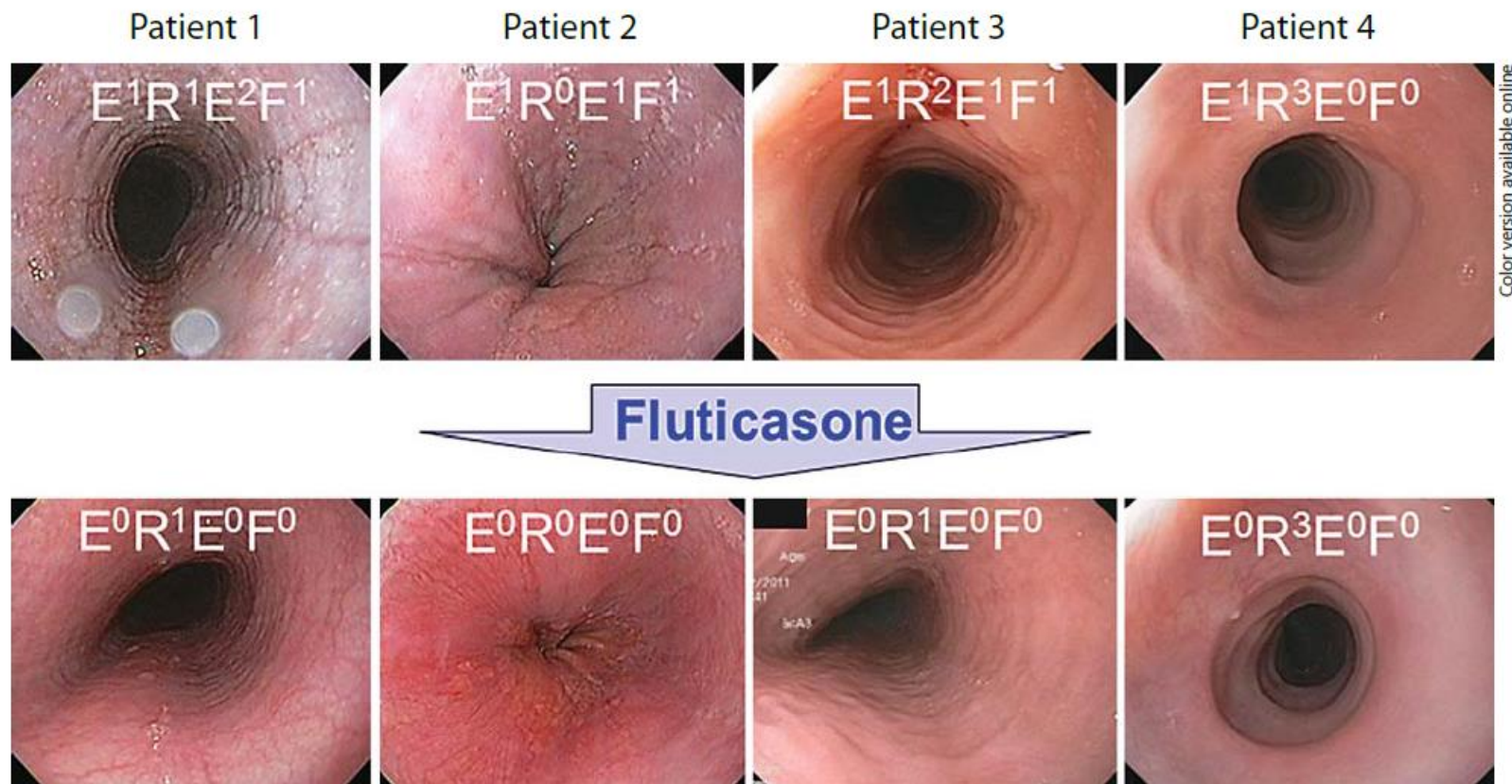


Fig. 1. Endoscopic images and corresponding endoscopic scores (EREFS) for esophageal mucosal findings prior to and after therapy with swallowed, topical fluticasone.

EEO – Corticoides

Corticoides tópicos isolados ou em combinação com a dieta, 4-12 semanas

Fluticasona tópica

- Formulação para a asma (MDI), que o doente deglute
- Não pode comer nem beber nada nos 30 minutos após
- Dose a ser ajustada em função idade e resposta clínica
- Risco de candidíase esofágica

Budesonido oral (viscoso)

- Efeito sobre a mucosa parece mais duradouro
- Mesmos cuidados que Fluticasona

Avaliação da eficácia (clínica, endoscópica e histológica)

Após controlo da inflamação, usar a dose mais baixa possível

Corticoide sistémico: alívio rápido, disfagia severa, estenose, desidratação, etc

Table 3. Eosinophilic esophagitis therapy

	Description	Use
Elemental diet	Diet is based on elemental formula	Currently used for short-term treatment of EoE to 1) induce rapid resolution of EoE in almost all patients (adult and children) 2) to establish food allergy
Six food elimination diet (SFED)	Most allergenic foods (milk, soy, egg, wheat, tree nuts, peanuts, fish, shellfish) are eliminated	Effective in about 70% of adult and pediatric patients
Targeted diet with allergy tests	Food eliminated based on skin tests and milk (often only 1–2 foods are eliminated)	Effective in 80% of children, limited studies in adults
Proton pump inhibitors (PPI)	1 mg/kg (20–40 mg max dose) 1–2 times a day	Given to everybody 8 weeks prior to diagnostic EGD May work as a stand alone therapy in PPI responsive EoE
Oral steroids	1 mg/kg twice a day for 10–15 days	Very effective short-term treatment used for emergency therapy of food impaction or debilitating symptoms (failure to thrive, protracted vomiting)
Swallowed steroids	Fluticasone 110–220 mcg two puffs twice a day. Budesonide 0.5–2 mg a day	Effective 50–70% of patients
Anti-IL5	Reslizumab Mepolizumab	Significantly reduce eosinophilic infiltration in the esophagus, no effects on symptoms
Anti-IgE	omalizumab	Not effective
Anti-tumor necrosis factor (TNF) α	Infliximab	Not effective
Anti-CRTH2	OC000459	Partially effective
Anti-IL-13	QAX576	Partially effective
Anti-TSLP	AMG 157	Future for EoE effective on asthma
Food allergy immunotherapy	EPIT	Future for EoE effective for IgE-mediated food allergy (peanut)

Outras Terapêuticas...

Anti-Leucotrienos (Montelukast)

Cromoglicato dissódico

Terapêutica Biológica

- **Anti - IL 5 (Mepolizumab e Reslizumab)**
- **Anti - TNF (Infliximab)**
- **Anti- IgE (Omalizumab)**

Imunoterapia Oral

- **Não recomendada**
- **Pode desencadear EEO...**

D. Gastrointestinais Eosinofílicas

Não há Guidelines publicadas...

O envolvimento da alergia é < que na EEO

A dieta de evicção dá menos resultados que na EEO

Frequentemente é necessário recorrer a corticoides

Vigilância apenas clínica? Endoscópica?

Patologias raras mas de reconhecimento crescente

História natural?

Dúvidas e futuro

História natural dos Distúrbios Eosinofílicos do tubo digestivo

Objectivos terapêuticos

Cura clínica?

Cura endoscópica?

Cura histológica?

Terapêutica de manutenção

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*DEDICATED TO IMPROVING THE LIVES OF INDIVIDUALS WITH
EOSINOPHILIC GASTROINTESTINAL DISORDERS*

CEGiR STUDY 7801

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7801: OMEGA - A Prospective, Multicenter Study to Compare and Validate Endoscopic, Histologic, Molecular, and Patient-Reported Outcomes in Pediatric and Adult Patients with Eosinophilic Esophagitis (EoE), Gastritis (EG) and Colitis (EC)

CEGiR is currently **RECRUITING** for the following clinical trial:

OMEGA



Learn about all the
benefits of joining the
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Bom congresso!

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Coimbra
25 e 26 de
novembro de
2016

SAÚDE ORAL

ALIMENTAÇÃO
DO PREMATURO

GLÚTEN

DOENÇA
INFLAMATÓRIA
INTESTINAL

PORFIRIA
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HELICOBACTER
PYLORI

EIXO FÍGADO-
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Fig. 2. Natural course of EoE: retrospective study in 200 adult EoE patients [16].

