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European Society of Neurogastroenterology and Motility

UNIVERSITÀ DEGLI STUDI DI MILANO

EOSINOPHILIC ESOPHAGITIS

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Roberto PENAGINI (Milan)

Edoardo SAVARINO (Padua)

DIAGNOSIS AND TREATMENT ODF EOSINOPHILIC ESOPHAGITIS: *Italian guidelines*

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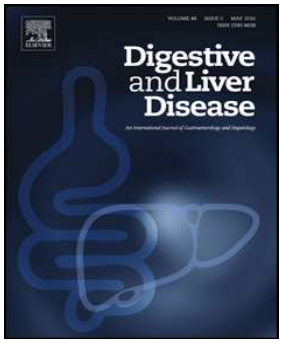
IN SUPREMÆ DIGNITATIS 1343

Position Paper

Eosinophilic esophagitis: Update in diagnosis and management. Position paper by the Italian Society of Gastroenterology and Gastrointestinal Endoscopy (SIGE)

Nicola de Bortoli[a,*], Roberto Penagini[b], Edoardo Savarino[c], Santino Marchi[a]



Dig Liver Dis. 2017 Mar;49(3):254-260

Statement 1. EoE is currently defined as a chronic, immune-mediated esophageal disease characterized by symptoms related to esophageal dysfunction and eosinophil-predominant inflammation .

Recommendation: strong; Evidence: moderate

Statement 3. EoE is a condition with an apparent increase of incidence.

Recommendation: strong; Evidence: moderate

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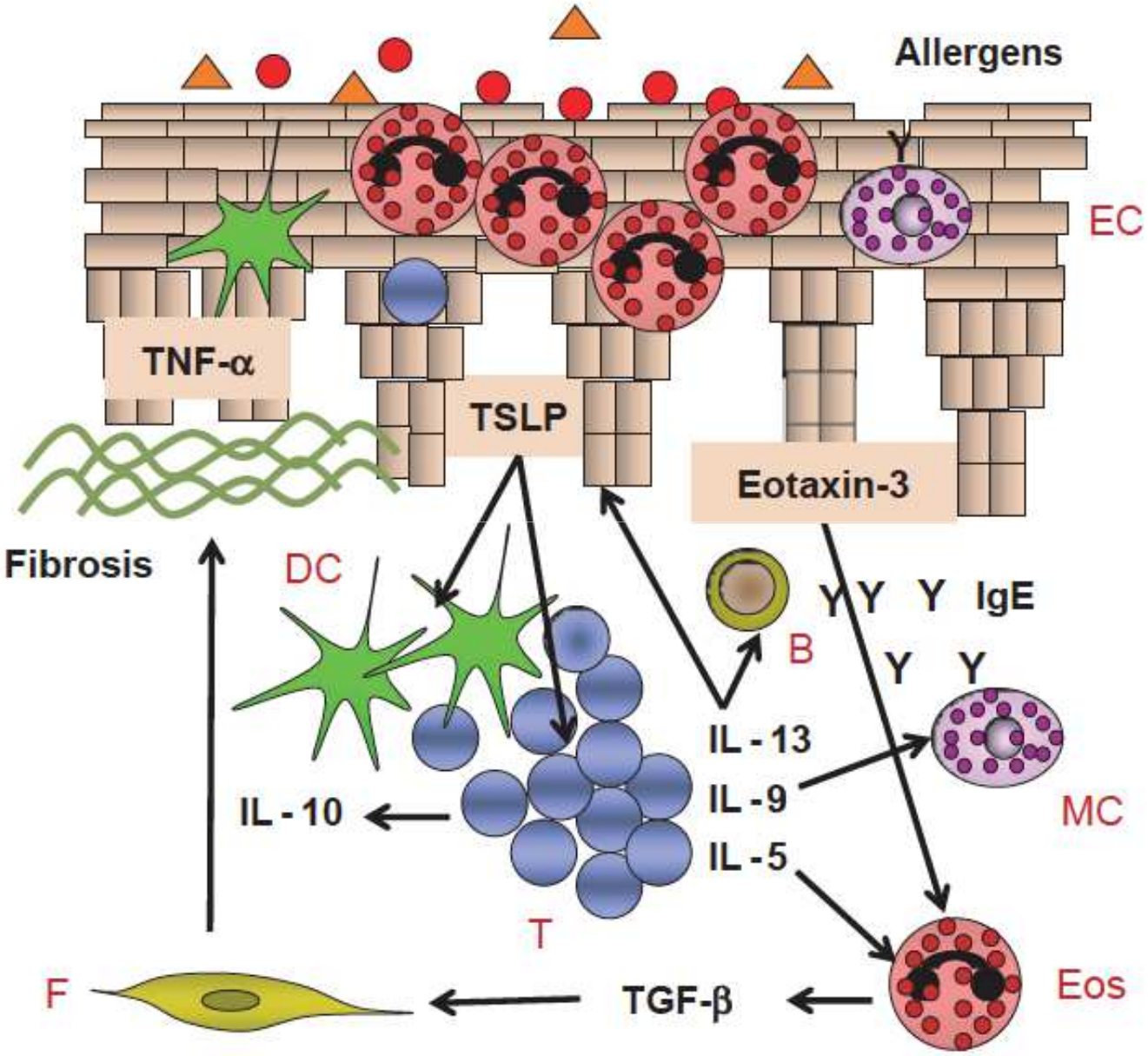
Epidemiological features

- EoE can occur at any age, with its prevalence reported to be similar in children and adults (≈ 0.5–1 cases/1000 persons).
- Incidence is estimated around 5–7/100.000 inhabitants/year (Europe and US).
- EoE occurs in male and female with estimated 3:1 ratio.
- EoE may occur at any age with a rising incidence in children with age and a peak in adults at 30–50 yrs
- White Americans and European seem most affected (58%) than African Americans (34%) or other ethnic groups (8%).

Ronkainen J et al. Gut2007;56:615–20.
Dellon ES et al. Clinical Gastroenterology and Hepatology 2014;12:589–96.
Syed AA et al. Aliment Pharmacol Ther 2012;36:950–8.
Weiler T et al. J Allergy Clin Immunol Pract 2014;2:320–5.



CELLS
EC: epithelial cells
DC: dendridic cells
Eos: eosinophilic cells
MC: mast cells
F: fibroblasts
T: Th2 lynphocytes
B: Lynphocytes B

MEDIATORS
IL: interleukines (5, 9, 10, 13)
TGF-β:
TNF-α: tumor necrosis factor alpha
TSLP: thymic stromal limphoprotein

- EoE patients usually suffer from a high number of concomitant **atopic disorders** including :
  - **Allergic rhinitis (OR 5.58; 95% CI 3.27–9.53)**
  - **Bronchial asthma (OR 3.06; 95% CI 2.01–4.66)**
  - **Eczema (OR 2.86; 95% CI 1.88–4.36).**

- **Food and aeroallergens** seem to have the same ability to support the disease and in causing exacerbations

Mishra Aet al. J Clin Invest 2001;107:83–90.
Mishra A et al. Gastroenterol 2003;125:1419–27.
Gonsalves N et al. Gastroenterol 2012;142:1451–9.
Straumann A et al. Allergy 2012;67:477–90.

Statement 6. Patients with EoE may present a wide range of symptoms, including dysphagia, bolus impaction, heartburn and chest pain. The clinical presentation may be very different according to the age of onset.

Recommendation: strong; Evidence: moderate

Dig Liver Dis. 2017 Mar;49(3):254-260

CLINICAL PRESENTATION

(in adults)

- Dysphagia for solids (25 to 100%)
- Food-impaction
- Chest pain
- Heartburn, Regurgitation
- Abdominal pain
- Allergic rinitis, bronchial asthma, eczema

(in children)

Abdominal pain -
Chest pain/Heartburn -
Decresed appetite -
Food refusal -
Chews food finely -
Holds food in mouth for 15 min -

ISSUE 1

If a patient with esophageal eosinophilia responded to proton pump inhibitors we should consider that he/she has GERD and not eosinophilic esophagitis?

YES

NO

ISSUE 2

Proton pump inhibitor therapy in patients with esophageal eosinophilia may reduce symptoms but it has no effect on eosinophilic infiltration and inflammation.

TRUE

FALSE

Statement 2. Proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) should be diagnosed when patients have esophageal symptoms and histological findings of EoE, but achieve clinical and histological remission on PPI therapy. The latest guidelines suggest that PPI-REE represents a clinical entity belonging to the clinical spectrum of EoE and this term should no longer be used

Recommendation: strong; Evidence: moderate

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Since 2011, solid evidence, mostly from adult patients, has highlighted that **PPI-REE and EoE are virtually indistinguishable** from one another, even at the genetic level, and very different from GERD.

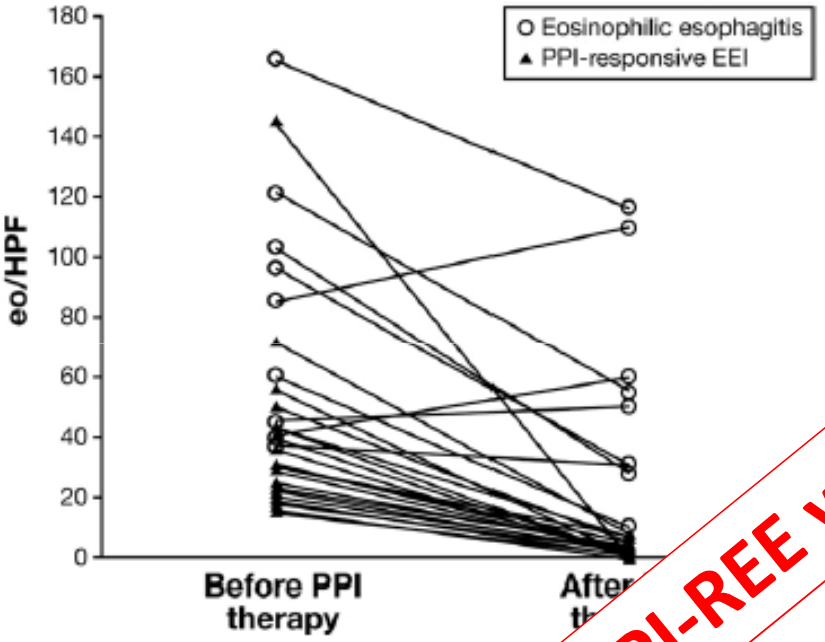
No other inflammatory disease than PPI-REE is defined by its response to a single medication, instead of by its **clinic**, **endoscopic**, **bioptic**, **molecular**, **genetic**, and **therapeutic** overlap with EoE.

Molina-Infante J et al Gut 2016; 65: 524–531.
Molina-Infante et al Clin Gastroenterol Hepatol 2011; 9: 110–117.

Esophageal Eosinophilic Infiltration Responds to Proton Pump Inhibition in Most Adults

JAVIER MOLINA-INFANTE,* LUCIA FERRANDO-LAMANA,‡ CRISTINA RIPOLL,§ MOISES HERNANDEZ-ALONSO,* JOSE M. MATEOS,* MIGUEL FERNANDEZ-BERMEJO,* CARMEN DUEÑAS,* NURIA FERNANDEZ-GONZALEZ,‡ EVA M. QUINTANA,‡ and MARIA ANGELES GONZALEZ-NUÑEZ‡

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2011;9:110–117

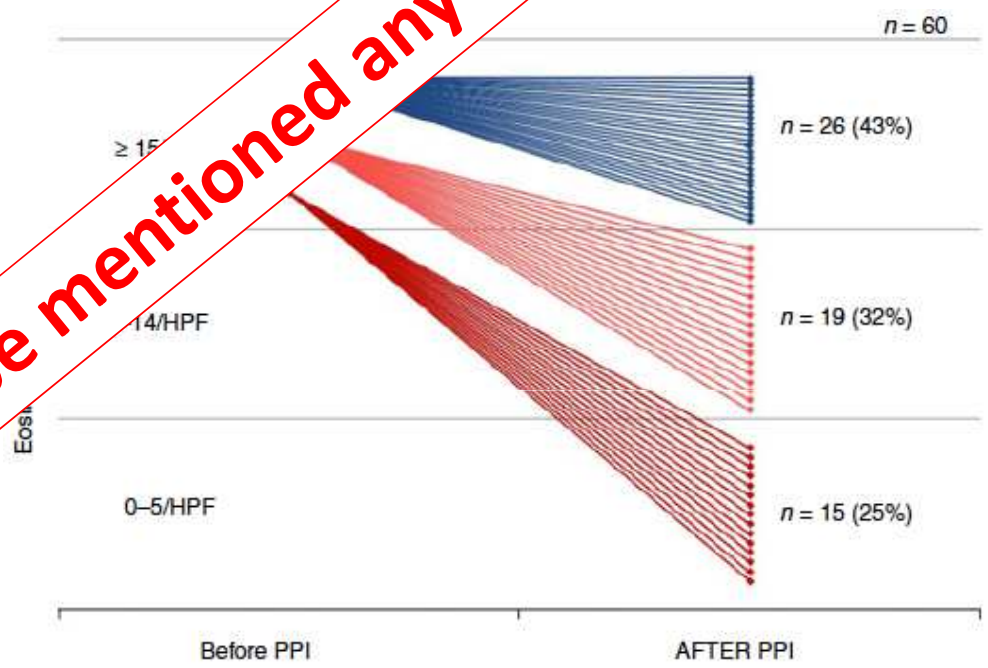


CONCLUSIONS:
In adults with EEI, 75% of unselected [illegible] 50% with an EoE phenotype respond to PPI therap[illegible]ing is poorly predictive of response. Patients with PPI-re[illegible]>35 eo/HPF are phenotypically undistinguishable from EoE[illegible]oE might be overestimated without clinical and pathologic follow-[illegible] patient response to PPI.

The outcome of patients with oeso[illegible]al eosinophilic infiltration after an eight-week t[illegible]oton pump inhibitor

G. Vazquez-Elizondo*, S. Ngamruengphong*, M. Kh[illegible]*, N. J. Talley* & S. R. Achem*

Alimen[illegible]r Ther 2013; 38: 1312–1319



CONCLUSIONS
More than 50% of patients with documented oesophageal eosinophilic infiltration in the EoE range improved when treated with a double-dose PPI trial for 8 weeks. These findings support the published guidelines recommending a PPI trial prior to diagnosing EoE, and confirm the existence of an eosinophilic oesophageal infiltrationPPI-responsive population.

The term PPI-REE will not be mentioned any longer.

ISSUE 3

The bioptic protocol to diagnose eosinophilic esophagitis consist of 3 or more biopsies both in cranial and in distal esophagus

TRUE

FALSE

ISSUE 4

In order to diagnose eosinophilic esophagitis, biopsies should be collected only when mucosal abnormalities (rings, furrows) are detected during endoscopy

TRUE

FALSE

ISSUE 5

When eosinophilic esophagitis is suspected, biopsy samples from stomach and duodenum should be collected.

TRUE

FALSE

Statement 7. Upper endoscopy with multiple esophageal biopsies must be the first step in the diagnostic approach to patients with suspected EoE, as well as in patients with dysphagia.

Recommendation: strong; Evidence: moderate

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- At least 6 biopsies should be obtained from at least two different locations in the esophagus in the distal and proximal halves of the esophagus.
- Inflammatory changes in EoE are frequently patchy and may not be present in all biopsies
- Diagnostic sensitivity increases with the number of biopsies and is maximized after taking at least six biopsies
- Esophageal biopsies should be targeted to areas of endoscopic abnormality, mainly white exudates and longitudinal furrows

Gonsalves N et al Gastrointest Endosc 2006;64:313–319.
Shah A, et al. Am J Gastroenterol 2009;104:716–721.
Peery AF, et al. Clin Gastroenterol Hepatol 2011;9:475–480.

Major features

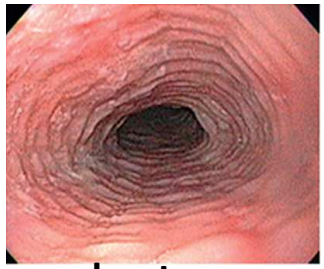
- **Fixed rings** (also referred to as concentric rings, corrugated oesophagus, corrugated rings, ringed oesophagus, trachealisation)
  - Grade 0: none
  - Grade 1: mild (subtle circumferential ridges)
  - Grade 2: moderate (distinct rings that do not impair passage of a standard diagnostic adult endoscope (outer diameter 8–9.5 mm))
  - Grade 3: severe (distinct rings that do not permit passage of a diagnostic endoscope)
- **Exudates** (also referred to as white spots, plaques)
  - Grade 0: none
  - Grade 1: mild (lesions involving <10% of the oesophageal surface area)
  - Grade 2: severe (lesions involving >10% of the oesophageal surface area)
- **Furrows** (also referred to as vertical lines, longitudinal furrows)
  - Grade 0: absent
  - Grade 1: present
- **Oedema** (also referred to as decreased vascular markings, mucosal pallor)
  - Grade 0: absent (distinct vascularity present)
  - Grade 1: loss of clarity or absence of vascular markings
- **Stricture**
  - Grade 0: absent
  - Grade 1: present

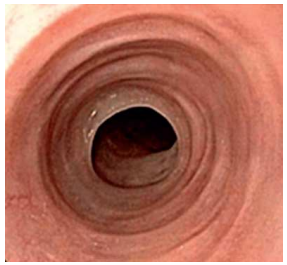
Minor features

- **Crepe paper oesophagus** (mucosal fragility or laceration upon passage of diagnostic endoscope but not after oesophageal dilation)
  - Grade 0: absent
  - Grade 1: present

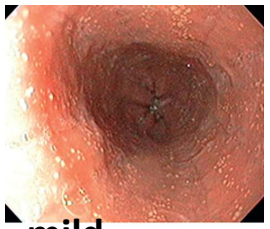
Hirano I et al. Gut 2013;62:489–495

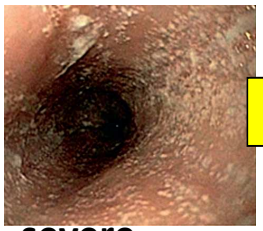

mild


moderate


severe

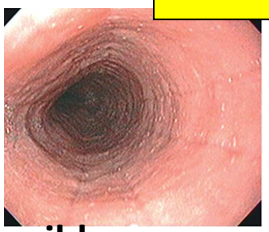
FIXED RING


mild

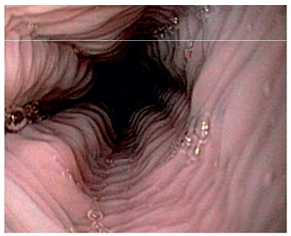

severe

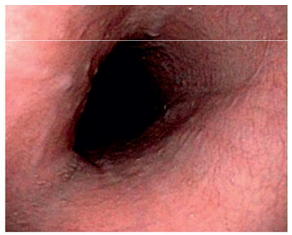
WHITE EXUDATES

FURROWS

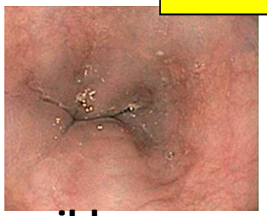

mild

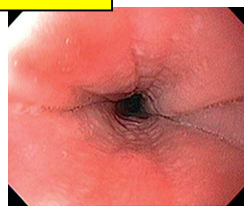

severe

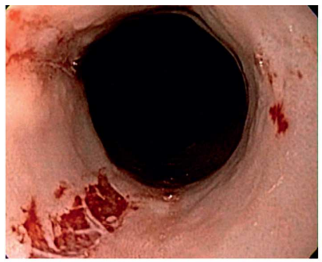

Time 0

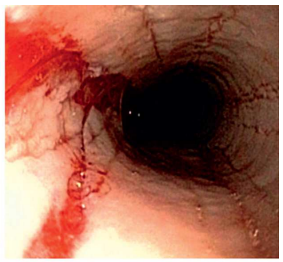

Time 1 (with insufflation)

OEDEMA


mild

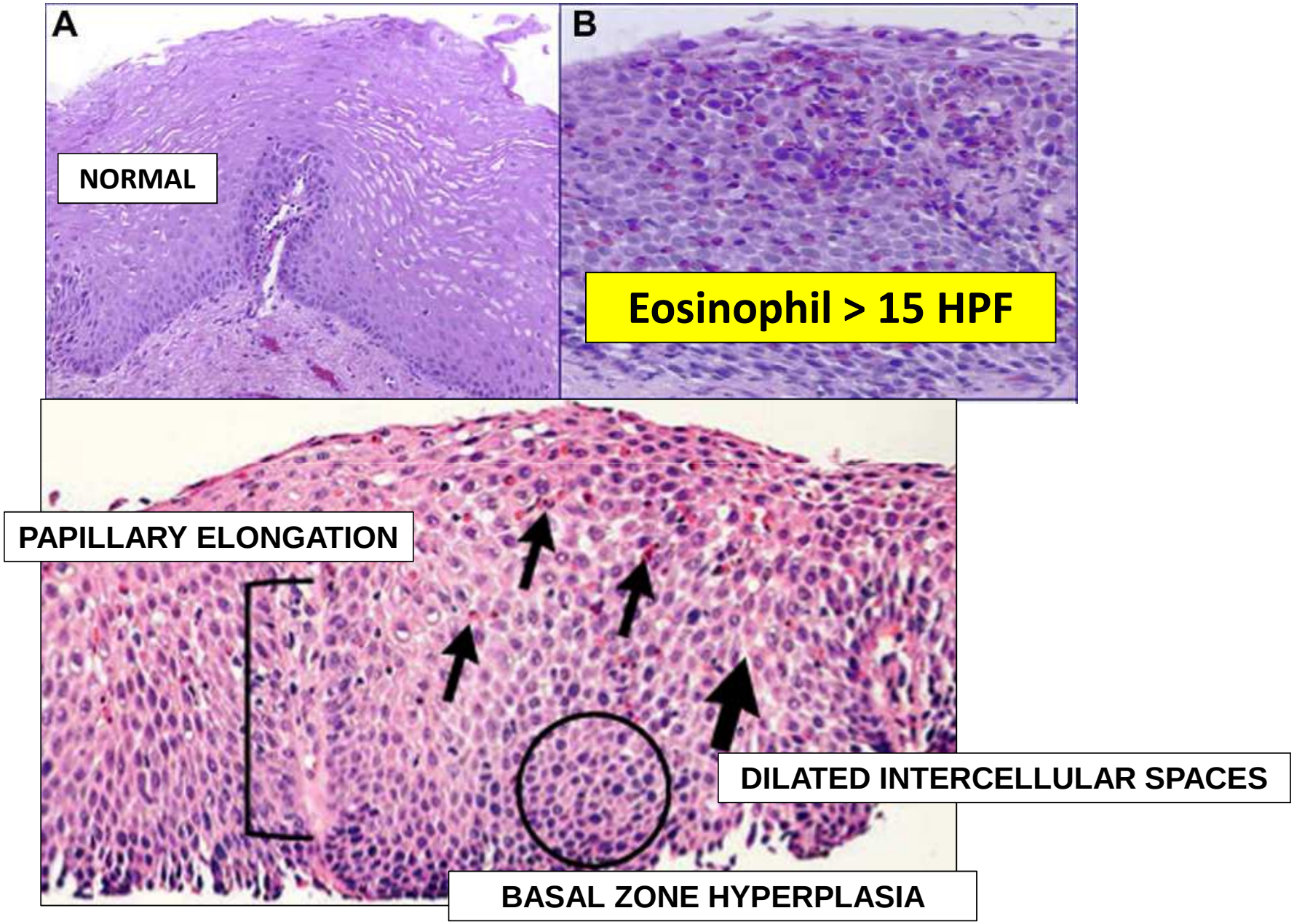

severe





CREPE-PAPER ESOPHAGUS

HISTOLOGIC DIAGNOSIS



ISSUE 6

When eosinophilic esophagitis is diagnosed and treatment is started, clinical symptomatic relief is sufficient in order to consider the patient as a “responder”

TRUE

FALSE

Statement 9. Endoscopy with biopsy should be performed in order to assess the effectiveness (eosinophils <15/HPF) of PPIs, dietary and/or steroid therapy. In addition, endoscopy should be repeated in case of reintroduction of foods after dietary elimination to identify triggers of esophageal inflammation and symptoms.

Recommendation: conditional; Evidence: low

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Symptom resolution cannot be considered a sufficiently reliable parameter to define the remission of the disease.

ISSUE 7

When eosinophilic esophagitis is diagnosed, pH or multichannel impedance and pH (MII-pH) monitoring is not needed in order to select patients for proton pump inhibitors treatment

TRUE

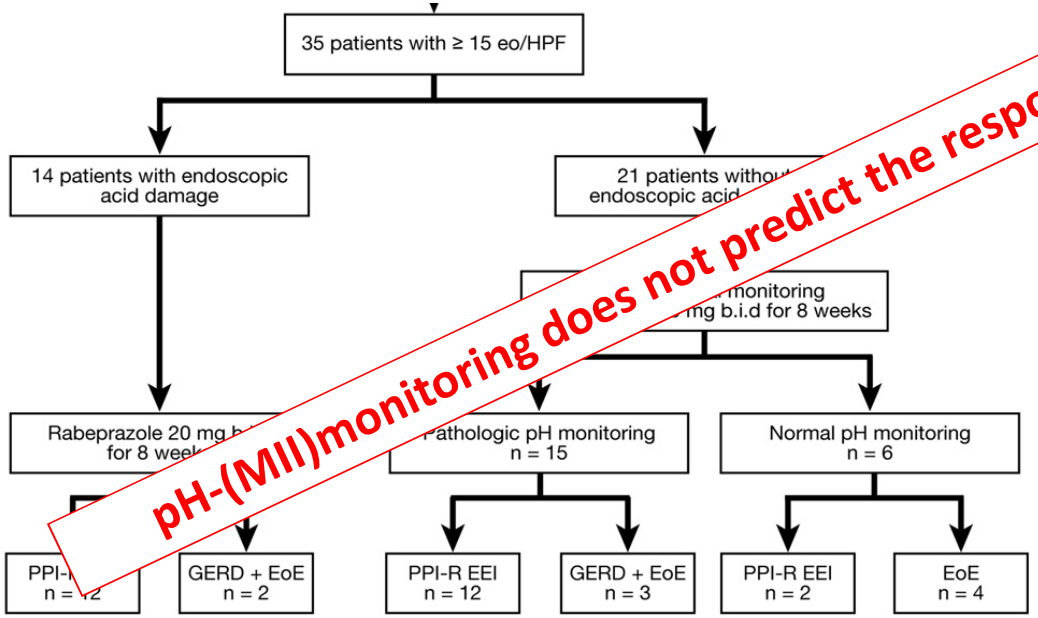
FALSE

Statement 10. Some additional tests may be useful to complete and confirm the diagnosis of EoE.

Recommendation: conditional; Evidence: low

Dig Liver Di... Mar;49(3):254-260

pH-(MII)monitoring does not predict the response of esophageal eosinophilia to PPI therapy



Molina-Infante J et al Clin Gastroenterol Hepatol 2011;9:110–117

Eosinophilic esophagitis: Updated consensus recommendations for children and adults

Chris A. Liacouras, MD, Glenn T. Furuta, MD, Ikuo Hirano, MD, Dan Atkins, MD, Stephen E. Attwood, MD, FRCS, FRCSI, MCh, Peter A. Bonis, MD, A. Wesley Burks, MD, Mirna Chehade, MD, Margaret H. Collins, MD, Evan S. Dellon, MD, MPH, Ranjan Dohil, MD, Gary W. Falk, MD, MS, Nirmala Gonsalves, MD, Sandeep K. Gupta, MD, David A. Katzka, MD, Alfredo J. Lucendo, MD, PhD, Jonathan E. Markowitz, MD, MSCE, Richard J. Noel, MD, Robert D. Odze, MD, FRCP, Philip E. Putnam, MD, FAAP, Joel E. Richter, MD, FACP, MACG, Yvonne Romero, MD, Eduardo Ruchelli, MD, Hugh A. Sampson, MD, Alain Schoepfer, MD, Nicholas J. Shaheen, MD, MPH, Scott H. Sicherer, MD, Stuart Spechler, MD, Jonathan M. Spergel, MD, PhD, Alex Straumann, MD, Barry K. Wershil, MD, Marc E. Rothenberg, MD, PhD,* and Seema S. Aceves, MD, PhD* *Aurora*

Committee clinical recommendations. Esophageal pH monitoring (and pH impedance, where available) is a useful diagnostic test to evaluate for GERD in patients with esophageal eosinophilia. Other testing modalities do not yet offer clear clinical benefit in diagnostic testing.

J Allergy Clin Immunol. 2011 Jul;128(1):3-20

ISSUE 8

The first line therapeutic approach in patients with eosinophilic esophagitis is topical steroid treatment

TRUE

FALSE

Statement 11. The first line treatment of EoE is represented by PPIs; in case of no response, the treatment continues with topical steroids and dietary elimination.

Recommendation: strong; Evidence: moderate

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Considering their favorable safety profile, ease of administration, and high response rates, PPIs must be considered as first-line therapy in patients with EoE.

A PPI double dose is usually prescribed for at least 8 weeks to assess the response to PPIs.

Topical steroids and dietary therapy are considered the next step for the treatment of EoE

Molina-Infante J et al. Clin Gastroenterol Hepatol 2011;9:110–117
Lucendo AJ et al. Clin Gastroenterol Hepatol. 2016 Jan;14(1):13-22

ISSUE 9

Endoscopic dilatation in patients with eosinophilic esophagitis should never be performed due to the high risk of esophageal complications (bleeding and perforation)

TRUE

FALSE

Statement 13. Endoscopic esophageal dilation may be used as an effective therapy in symptomatic patients with strictures that persist in spite of medical or dietary therapy and in patients with severe esophageal stenosis, endoscopically documented at onset of symptoms.

Recommendation: strong; Evidence: moderate

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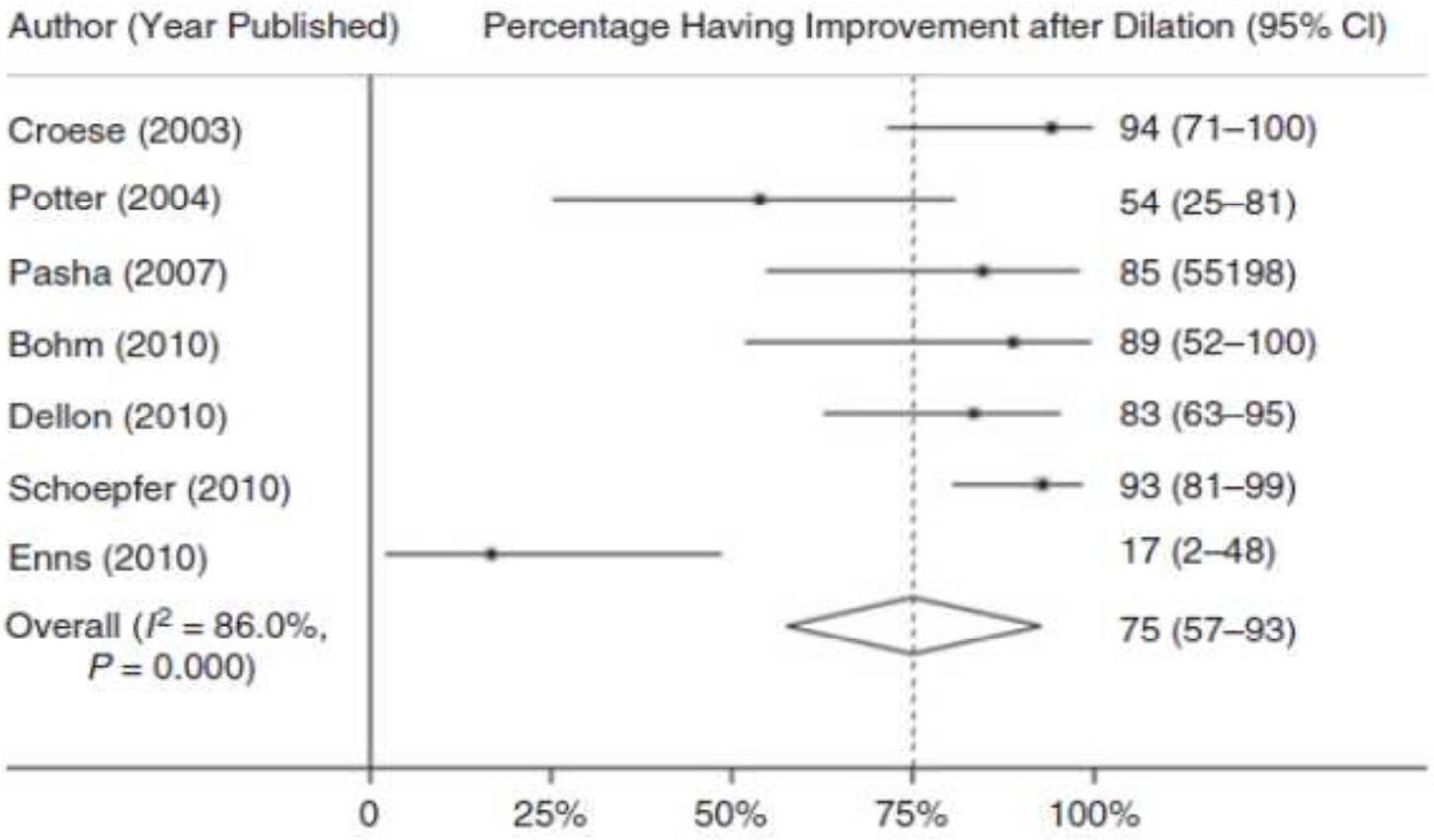
The risk of perforation as a result of the esophageal dilation is very low, and certainly lower than that reported from case studies in 1990 to 2000. Today, it is considered an effective and safe procedure

The risk of esophageal perforation smaller than 1%.

Aliment Pharmacol Ther 2013; 38: 713-720

Meta-analysis: the safety and efficacy of dilation in eosinophilic oesophagitis

F. J. Moawad*,†, J. G. Cheatham*,† & K. J. DeZee†,‡



Aliment Pharmacol Ther 2013; 38: 713-720

…in conclusion…

- EoE is a chronic, immuno-mediated disease characterized by symptoms related to esophageal dysfunction and eosinophilic infiltration.
- Upper endoscopy with 6 or more esophageal biopsies (upper and lower). Gastric and duodenal biopsies are advisable at diagnosis.
- Double dose PPI treatment for at least 8 weeks is the first line therapeutical approach.
- Symptom resolution cannot be considered a sufficiently reliable parameter to define the remission of the disease. Upper endoscopy and esophageal biopsies are needed.
- Topical steroids and dietary therapy are considered the next step for the treatment of EoE.