FDA Eosinophilic Esophagitis Workshop

College Park, September 19, 2012

NATURAL HISTORY OF

ADULT EOSINOPHILIC ESOPHAGITIS

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Eosinophilic esophagitis represents a chronic, immune/antigen-mediated esophageal disease, characterized **clinically** by symptoms related to esophageal dysfunction and **histologically** by eosinophil predominant inflammation.
“The **natural course** of a disease from the time immediately prior to its inception, progressing through its **presymptomatic phase** and different clinical stages to the point where it has ended and the patient is either cured, chronically disabled or dead **without external intervention**”

Posada de la Paz M; Groft SC. 2010. *Rare diseases epidemiology*. Vol. 686
...presymptomatic phase... => diagnostic delay

Levels

Clinical activity

Biochemical activity

Endoscopic activity

Histologic activity
EoE disease course

First EoE symptoms

Physician visit due to EoE symptoms

Interval 1
Time from first symptoms to physician visit

Interval 2
Time from physician visit to EoE diagnosis

EoE diagnosis

Mean diagnostic delay 4 years

“The **natural course** of a disease from the time immediately prior to its inception, progressing through its presymptomatic phase and different clinical stages to the point where it has ended and the patient is either cured, chronically disabled or dead **without external intervention**”

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NATURAL HISTORY OF
ADULT EOSINOPHILIC ESOPHAGITIS

QUESTIONS TO ADDRESS

1. What happens without therapy?
2. What are the long term consequences?
   (Organ damage? Dysplasia?)
3. Can therapies alter natural history?
What happens without therapy?

Intensity of Dysphagia and Inflammation over Time

30 Adults followed for a mean of 7.2 years

Intensity of Dysphagia and Inflammation over Time

% of Baseline

Years between diagnosis and follow up

Dysphagia
Eosinophilia
Dysphagia (linear)
Eosinophilia (linear)

“What happens without therapy?”

ANSWER: “EoE is here to stay”

Alexander JA, Katzka DA. CGH 2011;9:370-372
NATURAL HISTORY OF ADULT EOSINOPHILIC ESOPHAGITIS

QUESTIONS TO ADDRESS

1. What happens without therapy?
2. What are the long term consequences?
   (Organ damage? Dysplasia?)
3. Can therapies alter natural history?
Endoscopic manifestation at diagnosis
The story of two phenotypes

Inflammation

Stenosis

Anti-eosinophil medication

Diets

Dilation

Evolution of Crohn‘s disease

Cumulative Probability (%)

Inflammatory

Penetrating

Stricturing

Patients at risk:

N=2002 552 229 95 37

Months

Cosnes J, et al. Inflamm Bowel Dis. 2002;8:244-250
Swiss EoE database (SEED)

SEED CHARACTERISTICS

Head: Prof. Straumann, Olten County
Start: 1989 (prospective inclusions)
Catchment Area: entire Switzerland (8 millions)
Inclusion Criteria:
  clinical: esophageal dysfunction
  ≥ 15 eos/HPF since 2008
Differential-Dx: exclusion of other Dx leading to esophageal eosinophilia
Patients: 748 (9/2012)
**AIM:** to evaluate the relationship between disease duration and occurrence of strictures

**METHODS**

**Population:** patients of Prof. Straumann, n = 346

**Inclusion Criteria:**
- **clinical:** esophageal dysfunction
- **histology:** ≥ 24 eos/HPF 1989 – 2007
  ≥ 15 eos/HPF since 2008

**Differential-Dx:** exclusion of other Dx leading to esophageal eosinophilia

**Diagnosis:** established by Prof. Straumann

**Endoscopy:** ≥ 3 photos from index endoscopy

**Stricture definition:** passage of 9mm scope against resistance or not possible
Results stricture study

- 113 EoE patients (81% males)
- Mean age at index visit 41±14 years
- All caucasians
- Allergies in 70% of patients
- Median diagnostic delay 5.5 years (IQR 2-13.5, range 0-40 years)
- Predominant symptoms leading to Dx: Dysphagia (94%), chest pain (42%)
- Affected family member in 11%
Endoscopic presentation at EoE diagnosis

- 57% (64/113) with stenoses, single esophageal narrowing in 86%
- Mean stenosis diameter $10 \pm 3$ mm
- Mean stenosis length $2.7 \pm 2.5$ cm

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade</td>
<td>Can be passed by 9mm endoscope with resistance</td>
<td>78%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Cannot be passed with 9mm endoscope but with 6mm</td>
<td>16%</td>
</tr>
<tr>
<td>High-grade</td>
<td>Cannot be passed with 6mm endoscope</td>
<td>6%</td>
</tr>
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</table>
Endoscopic presentation at EoE diagnosis

- 27% with fixed rings, 73% with strictures
- Stenosis Location: 34% proximal, 66% distal
- Peak eos count did not change over time (49 ± 35 eos/HPF vs. 55 ± 43 eos/HPF)

<table>
<thead>
<tr>
<th>Esophageal diameter (cm)</th>
<th>3</th>
<th>2</th>
<th>1.5</th>
<th>1</th>
<th>0.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area (cm²)</td>
<td>7.1</td>
<td>3.1</td>
<td>1.8</td>
<td>0.79</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Area = \( \pi \times \text{radius}^2 \)
Risk for stenosis over time

Strictures at EoE diagnosis (%)

Disease duration (years), taking into account diagnostic delay

P = 0.002

<table>
<thead>
<tr>
<th>Disease duration</th>
<th>Strictures at EoE diagnosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>30</td>
</tr>
<tr>
<td>3-5</td>
<td>26</td>
</tr>
<tr>
<td>6-8</td>
<td>9</td>
</tr>
<tr>
<td>9-11</td>
<td>12</td>
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<tr>
<td>12-14</td>
<td>9</td>
</tr>
<tr>
<td>15-17</td>
<td>8</td>
</tr>
<tr>
<td>18-20</td>
<td>4</td>
</tr>
<tr>
<td>&gt;20</td>
<td>15</td>
</tr>
</tbody>
</table>

n
30 26 9 12 9 8 4 15
Consequences of remodelling

Eosinophilic Esophagitis: Analysis of 251 Adolescent and Adult Patients

ALEX STRAUMANN, \* CHRISTIAN BUSSMANN, § MARKUS ZUBER, § SIMONE VANNINI, || HANS-UWE SIMON, || ALAIN SCHOEPFER

\*Department of Gastroenterology, Kantonsspital Olten, Olten; \§Institute for Pathology, Violar Laboratory, Altewil; ||Department of Abdominal Surgery, Kantonsspital Olten, Olten; ||Department of Gastroenterology, University Hospital Bern, Bern; and ||Institute for Pharmacology, University of Bern, Bern, Switzerland

See Kapel RC et al on page 1316 for companion article in the May 2008 issue of Gastroenterology.

Background & Aims: Eosinophilic esophagitis is a rapidly emerging, chronic inflammatory disorder. Prolonged inflammation evokes structural alterations and a fragile esophageal wall prone to perforation/rupture and food impaction. This report assesses the risk of spontaneously arising and procedure-induced complications and proposes practical recommendations. Methods: The Swiss Esophageal Esophagitis Database documented 251 confirmed cases. A chart review identified which patients had required endoscopic bolus removal and/or experienced transmural esophageal perforation/rupture. In addition, a MEDLINE search for “eosinophilic esophagitis” with “esophageal perforation” or “esophageal rupture” was undertaken. Results: During an 18-year period, 87 patients (34.7%) experienced 134 food impactions requiring flexible (124, 92.5%) or rigid (10, 7.5%) endoscopic bolus removal. Transmural perforation occurred in 28% (2/10) of rigid procedures, and 1 esophageal rupture (Boerhaave’s syndrome) was observed. Conclusions: Bolus removal by rigid endoscopy is a high-risk procedure and should be avoided in eosinophilic esophagitis patients who require a factor for both superficial lacerations as well as even deeper lesions, including transmural perforation or rupture. This risk is illustrated by articles documenting 5 EE patients who incurred procedure-induced esophageal perforations9-11 and 2 patients cited in the literature who experienced spontaneous esophageal ruptures associated with a retching event.11,12 This report presents another 3 EE patients with esophageal breaches. On the basis of the experience of our long-term cohort and on a literature review, we propose practical recommendations for gastroenterologists and ear, nose, and throat (ENT) surgeons. Our goal is to reduce the risk of further procedure-related esophageal perforations and to help protect physicians from medicolegal issues when treating patients with dysphagia.

Methods

The Swiss EE Study Group consecutively enrolled patients presenting with a confirmed (by using clinical, endoscopic, and histologic methods) diagnosis into a Swiss EE Database, SEED, which was nationally established in 1989. Inclusion criteria are (1) PPI-resistant esophageal-related symptoms, (2) EE-consistent endoscopic abnormalities, (3) infiltration of the esophageal mucosa with at least 24 eosinophils/high-power field (HPF), and (4) informed consent.

We performed a chart review and included patients with persistent food impaction requiring bolus removal and those who experienced a "spontaneous" transmural esophageal rupt-
748 confirmed EoE (SEED 2012)

34.8% (260/748) long-lasting impactions (necessity of bolus removal)

362 endoscopic interventions (1.4 per patient, range 1-5)

340x by flexible endoscopy

22x by rigid endoscopy

Perforations transmural: 11/362 ≈ 3%, 11/260 ≈ 4.2%

- Retching-induced: 5
- Procedure-induced: 6 (4 rigid, 1 flexible, 1 dilation)

..... and none of these patients was adequately treated

Is EoE a precancerous lesion?


Liacouras CA, et al. JACI 2011;128:3-20

6 CR of Barrett esophagus and concomitant EoE (1 of them with low-grade dysplasia)

EoE not considered as a precancerous condition
(further data awaiting)
“What are long-term consequences?”

ANSWER

esophageal remodeling => bolus impaction => perforation risk

Further data needed regarding dysplasia risk
Can therapies natural history?

**Therapeutic Options 2012: DDD**

**Diet**
- Elemental Diet
- Elimination Diet (individually, allergy-testing based)
- Six-Food Elimination Diet

**Drugs**
- Corticosteroids systemically (e.g. prednisone)
- Corticosteroids topically (e.g. budesonide, fluticasone)
- Anti-Allergens (Leukotriene-Antagonists, CRTH2-Blocker)
- Biologicals (e.g. anti-IL5, anti-IL13)
- Immunosuppressant’s (e.g. azathioprine, 6-mercaptopurine)

**Dilation**
**Therapeutic Options 2012: DDD**

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**Dilation**
Long-lasting symptom improvement but does not change underlying inflammation

Symptom improvement, reduces eosinophil counts and subepithelial fibrosis

Kagalwalla A, et al. CGH 2006;4:1097-1102

Symptom improvement, reduces eosinophil counts and subepithelial fibrosis

Straumann A, et al. CGH 2011;9:400-409

Schoepfer AM, et al. AJG 2010;105:1062-1070
Histology (Van Gieson)

Control (esophagus healthy)

EoE Patient Pre-treatment

EoE Patient Post-treatment

EUS

Straumann et al. *Clin Gastro Hepatol* 2011
“Can therapy alter natural history?”

ANSWER
Drugs: maybe
Diets: maybe
Dilation: to crack strictures
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Thank you!

All International and Swiss Collaborators
Sponsors - TIGERS, SNSF, Aptalis, Astra-Zeneca, FALK, GSK, MSD, UCB