Eosinophilic Esophagitis

AUTHORS:

Prof. Dr. Alain Schoepfer
Department of Gastroenterology
and Hepatology
University Hospital Lausanne
CHUV
1011 Lausanne, Switzerland

Prof. Dr. Stephan Miehlke
Center for Digestive Diseases
Internal Medicine Center
Eppendorfer Landstraße 42
20249 Hamburg, Germany

and

Center for Esophageal Diseases
University Hospital Eppendorf
Martinistraße 52
20251 Hamburg, Germany

Prof. Stephen E Attwood
Durham University
Stockton Road
Durham DH1 3LE
United Kingdom

Publisher

DR. FALK PHARMA GmbH

Leinenweberstr. 5
79108 Freiburg
Germany

www.drfalkpharma.com

1st edition 2018

Eosinophilic Esophagitis (EoE)

Prof. Dr. Alain Schoepfer
Prof. Dr. Stephan Miehlke
Prof. Dr. Stephen Attwood

CONTENTS

GENERAL INFORMATION CONCERNING EoE

What is eosinophilic esophagitis?

Eosinophilic esophagitis (abbreviated EoE) is a chronic, inflammatory disease of the esophagus whose origins and causes are not yet fully understood. This inflammation of the esophagus (as denoted by the "itis" at the end of esophagitis) is characterized by the presence of a certain type of white blood cells in the mucosa, the so-called eosinophils. This is why the disease is called eosinophilic esophagitis. The most commonly reported symptoms include difficulty swallowing (whereby food may potentially become lodged in the esophagus) and pain during swallowing.

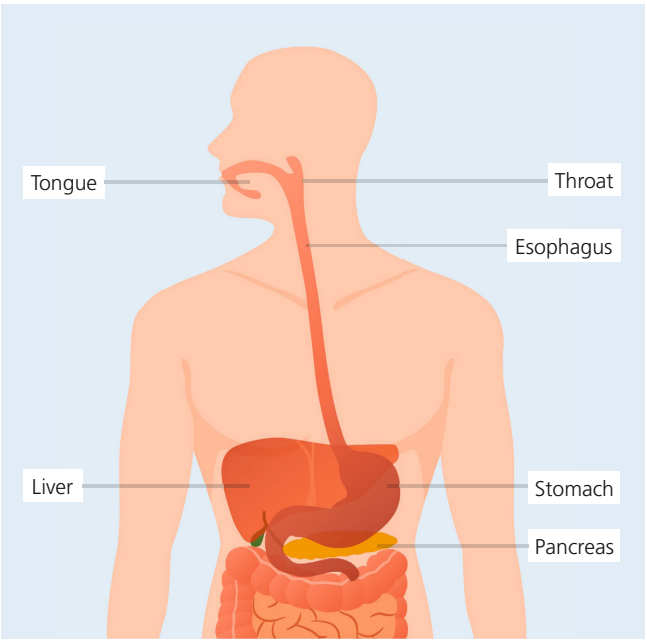


Fig. 1: The esophagus connects the mouth to the stomach

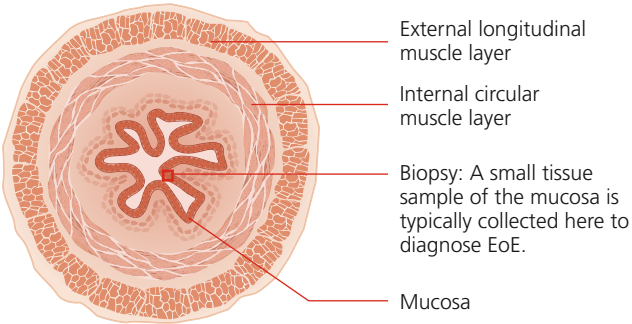


Fig. 2: Cross-section of the esophagus under a microscope

What are the causes of EoE?

The esophagus is about 25 cm long with a diameter of about 2.5 cm. It connects the oral cavity (or mouth) to the stomach and is responsible for transporting food from the throat to the stomach. Based on this function, the esophagus comes into contact with all of the food we consume.

In EoE patients, certain food components (so-called allergens) are suspected of triggering inflammation in the esophagus.

Common triggers of EoE include

- **Cow's milk (≥ 50%)**
- **Wheat (≥ 50%)**
- **Soya**
- **Eggs**
- **Nuts**
- **Fish and seafood**

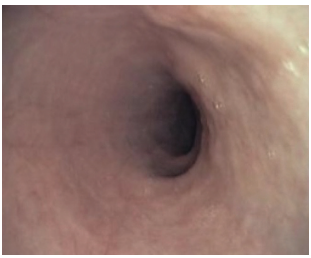
The inflammatory reaction is highly similar to asthma, a chronic, inflammatory condition of the respiratory tract that is triggered by allergens in the air. Therefore, EoE is often referred to as "asthma of the esophagus". As in the case of asthma, airborne allergens are also suspected of potentially triggering EoE.

EoE is presumed to involve a chronic, inflammatory reaction to certain allergens in foods and in the air.

In addition, EoE patients also commonly suffer from allergic diseases, such as hay fever, asthma or rash and food allergies in general. The connection between EoE and these disorders remains unclear. The exact causes and pathogenic processes of EoE are also not completely understood and thus form the focus of current research.

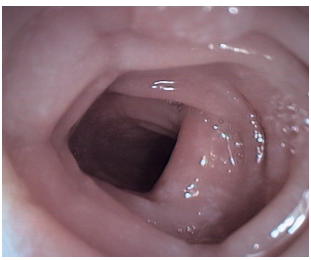
› What are the symptoms of EoE?

The main symptoms of EoE in adults include difficulty swallowing (so-called "dysphagia") and/or pain during swallowing, also known as "odynophagia". Usually the discomfort is felt in the chest, and less often in the lower neck or upper abdomen. In a worst-case scenario, EoE can even result in an obstruction of the esophagus, a so-called food bolus impaction, when a bite of food is consumed (see Figure 3). In some cases, the food can no longer be coughed up or regurgitated and requires removal from the esophagus by a physician. Affected persons often experience pain during swallowing, chest pain, and heartburn. In children, the symptoms are significantly less consistent and EoE often manifests indirectly with vomiting, reduced appetite or growth disorders. As a result, a diagnosis is often difficult and may be significantly delayed after the initial occurrence

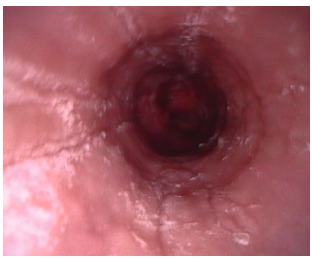


Normal

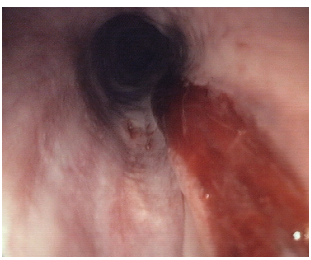
Inflammation: white deposits



Strictures (narrowing) with typical ring formation



Acutely inflamed EoE with lengthwise reddish furrows



Mucosal tear following successful dilatation

Obstruction of the esophagus with a piece of meat (arrow)

Fig. 3: Endoscopic findings in the esophagus. In about 10% of EoE patients, the esophagus appears normal despite the presence of microscopic inflammation. Signs of acute inflammation (white deposits, mucosal swelling, elongated striations) and signs of scarring (ring formations with narrowing of the diameter of the esophagus in some cases) are distinguished.

of symptoms – taking years in some cases.
In addition, pronounced avoidance strategies have been observed, especially in adolescent and adult patients, including:

- Avoidance of certain foods or even avoiding restaurants altogether.
- Thoroughly chewing food and consuming food in small bites only.
- Drinking copious amounts of liquid and doing so frequently in order to minimize or prevent difficulty during swallowing.

Although these avoidance strategies seriously restrict the quality of life, many patients are often unaware that they are suffering from a disease of the esophagus because they consider their condition to be normal.

If EoE remains untreated, the esophagus may often continue to constrict over the years (reducing the diameter of the esophagus). The difficulty swallowing typical of EoE is either the result of an active inflammation or a narrowing of the esophagus. This difficulty occurs especially with highly solid foods (see Figure 4). But it is also possible that a person never experiences difficulty swallowing and then the disease suddenly manifests when a piece of food becomes lodged in the esophagus.

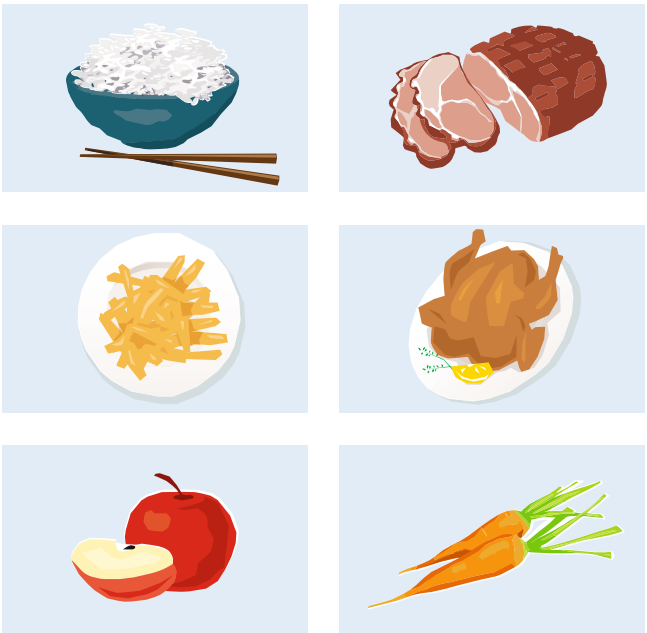


Fig. 4: Typical foods that trigger difficulty swallowing include dry rice, meat, raw fruits and vegetables (e.g. carrots, apples) or French fries. Patients experience difficulty swallowing because these foods are very solid, not because they trigger acute allergies.

› How can EoE be diagnosed?

EoE can only be definitively diagnosed by a gastroenterologist. In addition to the symptoms described above, EoE is diagnosed by endoscopic examination of the esophagus with simultaneous collection of tissue samples. The esophagus commonly exhibits signs of acute inflammation (see Figure 3), but only a high number of eosinophils in the mucosa of the esophagus is considered decisive evidence of EoE (see Figures 5 and 6).

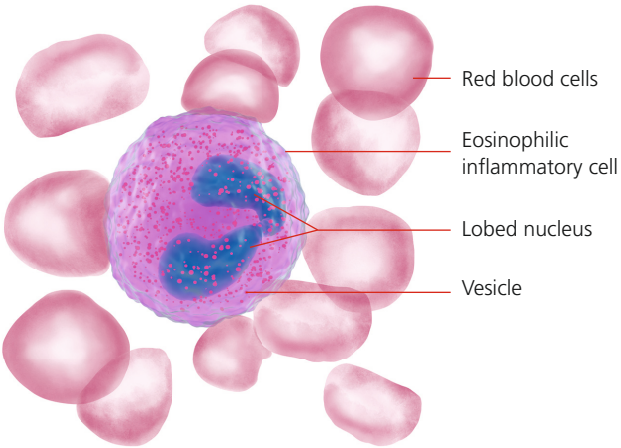


Fig. 5: Eosinophilic inflammatory cell in the blood. The eosinophilic inflammatory cell is surrounded by red blood cells. It has a lobed nucleus (purple) and many vesicles in which substances are stored that trigger inflammation when released. Every human has small numbers of eosinophilic inflammatory cells circulating in the blood. These form an important line of defense against parasites (e.g. worms) and in the case of allergies. The mucosa of the esophagus is normally completely free of eosinophilic inflammatory cells.

› How frequently does EoE occur?

EoE is a rare disorder that was first recognized as a disease in 1993. In Europe around 16 out of 100,000 inhabitants suffer from EoE, although there are large geographic variations.

› What are the risk factors for EoE?

The majority of patients with EoE are male (approx. 80%). EoE can occur at any age, but occurs most commonly between the ages of 30 and 50. Patients with EoE often suffer from other allergic diseases, such as hay fever, allergic asthma, food allergies or atopic dermatitis. Hereditary risk factors are known, but have no influence on the diagnosis or treatment of EoE.

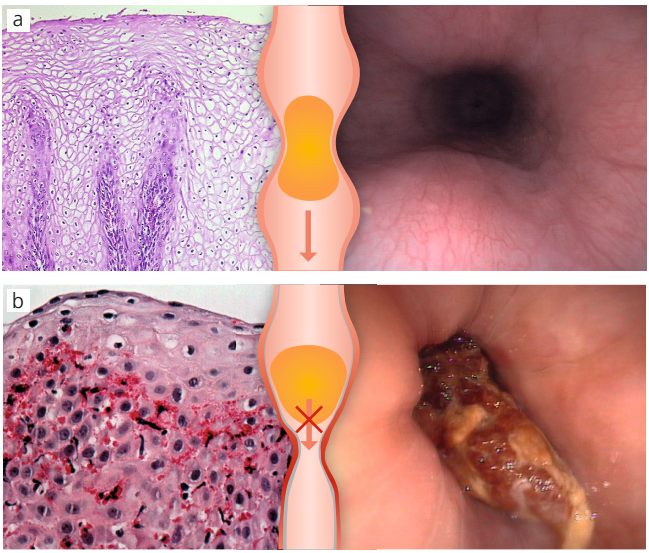


Fig. 6: a) Normal esophagus with no eosinophils
b) Increased eosinophils in an EoE patient

How does EoE progress if left untreated?

If EoE is left untreated, scarring of the esophagus may occur with a narrowing of the esophagus as the result of persistent inflammation over the years due to the presence of eosinophilic inflammatory cells (see Figure 6). EoE is a chronic disease for which there is currently no cure.

Various therapies can minimize narrowing and scarring, prevent complications, such as obstruction of the esophagus, and significantly improve the quality of life of patients.

THERAPEUTIC PRINCIPLES OF EoE

Three different treatment options are currently available: The first option involves medications (cortisone products and proton-pump inhibitors); the second option involves diets that avoid certain allergens; and the third option involves the dilation of the esophagus during an endoscopic procedure.

› Acute inflammation

Medications and diets are primarily applied in the case of acute inflammation. These therapies also have the advantage of minimizing the high risk of narrowing (also known as stricture formation) and potentially irreversible scarring of the esophagus associated with prolonged untreated cases of EoE.

› Advanced disease

If EoE has been diagnosed too late or the patient no longer responds to a medication or diet and severe narrowing of the esophagus results, then dilation is applied. Here, the constricted segment is carefully dilated during an endoscopic procedure with the patient under deep sedation (without general anesthesia). Patients are typically pain- and symptom-free within 2-3 days after this procedure.

The different treatment options are applied based on the clinical picture: Medications and diets in the case of acute inflammations, dilation in the advanced stage once the esophagus has already narrowed.

Long-term treatment is required

EoE is currently unable to be cured with medications or diet. Unfortunately, if inflammation-inhibiting therapies are discontinued, the inflammation commonly flares up after a few months accompanied by the known symptoms. As a result, the patient must remain in close contact with the treating physician, watch out for symptoms, and undergo regular check-ups.

But inflammation of the esophagus is not necessarily always accompanied by symptoms. It is possible to have mild forms of esophageal inflammation without ever noticing anything. An endoscopic follow-up examination of the esophagus should take place approx. 6-12 weeks following the start of treatment to verify therapeutic success.

Few approved treatment options

Due to the fact that EoE was not discovered until recently, only one medication has been officially approved to date for the treatment of EoE. It involves a locally acting cortisone product with the active ingredient budesonide, which is also known from asthma treatment. This product has been developed especially for the treatment of the esophagus. Although EoE involves an allergic reaction, anti-allergic agents or immunosuppressants are not recommended due to a lack of evidence of their efficacy.

DIFFERENT THERAPEUTIC OPTIONS

MEDICATIONS

Proton-pump inhibitors

Efficacy:
A minority of EoE patients respond to treatment with so-called proton-pump inhibitors. These medications suppress the formation of gastric acid and are approved for the treatment of heartburn and stomach ulcers but not EoE. The effect in EoE patients is probably not based on an inhibition of acid but may be an effect on the immune function in the esophageal wall.

Due to the fact that there are not yet any studies comparing the treatment with placebo, more conclusive statements concerning efficacy cannot be made.

Intake:
Standard therapeutic doses of proton pump inhibitors (PPIs) are used to treat some patients with Eosinophilic Esophagitis.

Side effects:
Proton-pump inhibitors are considered relatively safe. Among the most common side effects are headache, abdominal pain, constipation, diarrhea, flatulence, nausea/vomiting and fundic gland polyps (benign).

Treatment duration:
Proton-pump inhibitors are typically administered for 6-8 weeks, but the exact duration should be in agreement with your doctor. If the patient does not experience any improvement, then other treatment strategies, such as local treatment with a cortisone product or diet, must be considered.

Local budesonide treatment of the esophagus

Efficacy:

Budesonide acts directly on the mucosa of the esophagus and blocks multiple steps of the inflammation there. In addition, it is rapidly inactivated in the body (in the mucosa and in the liver, which it reaches through the bloodstream) and is thus very well tolerated.

About 90% of patients with active inflammatory EoE experience a significant reduction in symptoms within the first few weeks of this therapy and also a significant reduction or even disappearance of the eosinophilic inflammation in the esophagus.

Intake:

EoE used to be commonly treated with asthma sprays containing budesonide or similar active ingredients that were swallowed instead of inhaled. But because these medications were developed to treat the respiratory tract, they are not ideal for coating the esophagus. Therefore, orodispersable tablets were developed for the treatment of EoE that specifically coat the esophagus.

Side effects:

There is a slightly increased risk of fungal infections (Candida) in the oral cavity or esophagus. Fungal infections are relatively easy to treat with antifungal lozenges for a period of 3 days.

Treatment duration:

Budesonide treatment is typically applied for 6 weeks when the patient either has symptoms and/or the inflammation is active. Treatment may be extended to 12 weeks in patients who do not respond adequately to treatment within 6 weeks.

DIETS

Most EoE patients are allergic to more than one food. As a result, EoE is regarded as a special type of food allergy. If it is possible to eliminate the foods that cause an allergic reaction in the esophagus from the diet, then the symptoms and inflammation may disappear without the use of medications. The most common foods that cause eosinophilic inflammation of the esophagus include dairy products, wheat, eggs, soy, nuts, and fish/seafood (see Figure 7). Appropriate diets are therefore associated with massive restrictions on daily food choices and are rarely applied successfully over prolonged periods.

Fig. 7: Common food allergens

Amino-acid-based nutrient solutions

Efficacy:
This diet dispenses with all conventional foods and instead involves the intake of a special nutrient solution. As a result, this diet is free of any allergy-triggering proteins and consists solely of the basic building blocks of dietary proteins, so-called amino acids, and other nutrients. These amino acids are produced as liquid food. Such protein-free diets have been found to be over 90% effective in reducing inflammation in adults with EoE.

Procedure:
Adult patients are able to follow this diet at home, provided that they are able to drink the liquids. The taste is often described as unpleasant. Children/adolescents requiring treatment with an amino-acids-based diet usually do not tolerate the taste, which is why this diet is administered via a feeding tube during an inpatient hospital stay.

Side effects:
Most patients find this diet to be extremely restrictive because they are not permitted to eat anything else. Adult patients rarely choose this diet.

Treatment duration:
This type of diet may be successful for 1-2 months, but is hardly feasible as a long-term therapy based on the associated restrictions.

A diet of nutrient solutions is associated with a considerable loss of quality of life and is rarely feasible over the long term.

Empirical elimination diet

Efficacy:

An elimination diet based on allergy testing results in an improvement in symptoms in only a very small number of patients. Generally allergy tests are not specific and are often misleading.

Therefore, usually an empirical elimination diet is performed, which is based on excluding the 6 most common allergy-triggering foods with subsequent, controlled, step-wise reintroduction until the allergy-triggering "culprit" is identified. This diet has been proven effective in children and adults. Inflammation of the esophagus has been successfully normalized in over 70% of patients on this diet.

Procedure:

This diet involves the complete elimination of dairy products, wheat, eggs, soy, nuts, and fish/seafood from the diet for 6-8 weeks. An endoscopic examination of the esophagus is then performed, including the collection of tissue samples. In the best case the inflammatory cells have disappeared from the esophagus. The individual foods are then reintroduced one after the other at 8-week intervals. Another endoscopic examination of the esophagus is then performed at approximately 8 weeks following reintroduction of each new food category in order to determine whether it triggers an eosinophilic inflammation of the esophagus. This procedure is continued until all allergy-triggering foods have been identified. Once an allergy-triggering food has been identified, it is eliminated from the diet.

During multiple sessions, a dietitian provides patients with instructions and advice on how these foods may be avoided. The diet is conducted on an outpatient basis.

In order to reduce the number of endoscopic inspections, a so-called step-up elimination diet may also be used in some cases, in which the first 2 foods (usually dairy and gluten-containing grain products) are eliminated and if there is no response, then 4 or ultimately 6 foods are eliminated from the diet. This step-up approach is able to reduce the number of endoscopic inspections by about 20% on average.

Limitations:
It can take up to about a year to identify the allergy-triggering food(s). It is also possible that a patient may require up to 8 endoscopic examinations of the esophagus in order to identify the triggering allergens (see Figure 8). Each EoE patient must also attend multiple sessions with a dietitian when following the

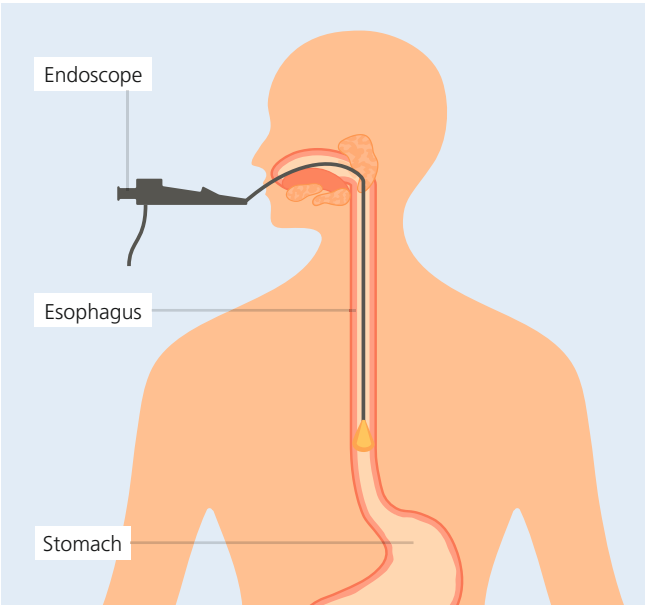


Fig. 8: Endoscopic examination of the esophagus

empirical elimination diet. Patients are not permitted to consume allergy-triggering foods over the long term. This is sometimes associated with restrictions on the quality of life.

Treatment duration:
Patients in whom the triggering foods are successfully identified are able to follow the diet over the long term (for months or years).

In many cases, the elimination diet may reduce symptoms and may also be maintained over a prolonged period.

DILATION OF THE ESOPHAGUS

Efficacy:
About 75% of patients, treated by dilatation, experience significantly improved symptoms within 12 months.

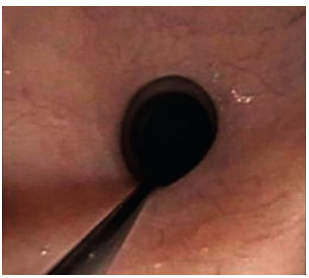
Procedure:
In the case of stricture formation (narrowing) of the esophagus, the diameter may be enlarged through dilation treatment. Here, an endoscopic examination is performed. The diameter of the esophagus is then enlarged by deploying an inflatable balloon or by inserting a wire into the stomach and advancing bougies (candle-shaped plastic cylinders) of increasing diameter into the esophagus via the instrument in use (endoscope).

Dilation takes about 10 minutes and is performed with the patient under deep sedation. The scar tissue that reduces the diameter of the esophagus is mechanically dilated during the procedure. However, this procedure does not treat the underlying inflammation that is causing the narrowing of the esophagus and dilation procedures must be repeated as new strictures form over time.

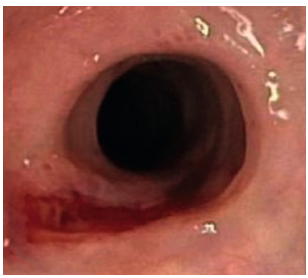
Side effects:
Pain during swallowing may occur in about half of the patients for 2-3 days following the procedure but this pain responds well to conventional pain relievers. The risk of complications, especially a hole (perforation) in the esophagus, is relatively low (<1%). A hole in the esophagus may be closed endoscopically with small metal staples or temporary stents that are then removed after a few weeks. Operations to treat the complications of dilation procedures are very rarely necessary.

Treatment duration:
Dilations may be performed as often as necessary. Patients are usually required to undergo dilation treatment once a year if they are not additionally receiving anti-inflammatory treatment with medications or a diet.

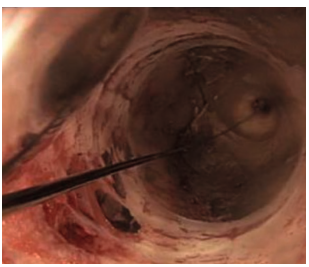
Dilation does not treat the causes of EoE, but instead merely involves the mechanical expansion of the constricted esophagus.



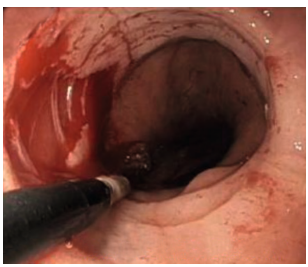
Stricture in the esophagus



Superficial laceration of the mucosa following attempted passage of a gastroscope



Insertion of an inflatable balloon via the accessory channel of the gastroscope. Balloon is inflated to a defined diameter.



The stricture is expanded, a superficial tear of the epithelium is visible. The gastroscope is then able to be pushed without difficulty.

Fig. 9

SUMMARY: CHARACTERISTICS OF THE DIFFERENT TREATMENTS

	MEDICATIONS	
	Proton-pump inhibitors	**Local steroid treatment of the esophagus**
Reduces symptoms	⊕⊕	⊕⊕⊕
Reduces endoscopically visible inflammation	⊕⊕	⊕⊕⊕
Reduces microscopically visible inflammation	⊕⊕	⊕⊕⊕
Reduces stricture formation (narrowing) in the esophagus	—	⊕
Side effects/limitations:	!	!
Notes	Effective in only a minority of EoE patients.	

Legend:

●●● Strong effect and/or many side effects

●● Moderate effect and/or moderate number of side effects

● Weak effect and/or few side effects

– No effect and/or no side effects

	DIETS			DILATION
	Amino-acid-based nutrient solutions	**Elimination diet based on allergy testing**	**Empirical elimination diet**	**Dilation treatment of the esophagus**
	⊕⊕⊕	⊕	⊕⊕	⊕⊕⊕
	⊕⊕⊕	⊕	⊕⊕	—
	⊕⊕⊕	⊕	⊕⊕	—
	—	—	—	⊕⊕⊕
	❗❗	—	—	❗
	Rarely used, usually administered via a feeding tube.	Roughly 30% chance that allergy testing will identify the triggering foods.	Roughly 70% chance that microscopically identifiable inflammation will be reduced. Multiple endoscopic examinations of the esophagus required to identify the triggering food(s).	No treatment of the underlying inflammation. Treatment must be repeated approximately once a year without additional dietary or medicinal treatment.

DR. FALK PHARMA GmbH

Leinenweberstr. 5
79108 Freiburg
Germany

JO80e 1-5/2018 Rau