

Eosinophilic Esophagitis



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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.

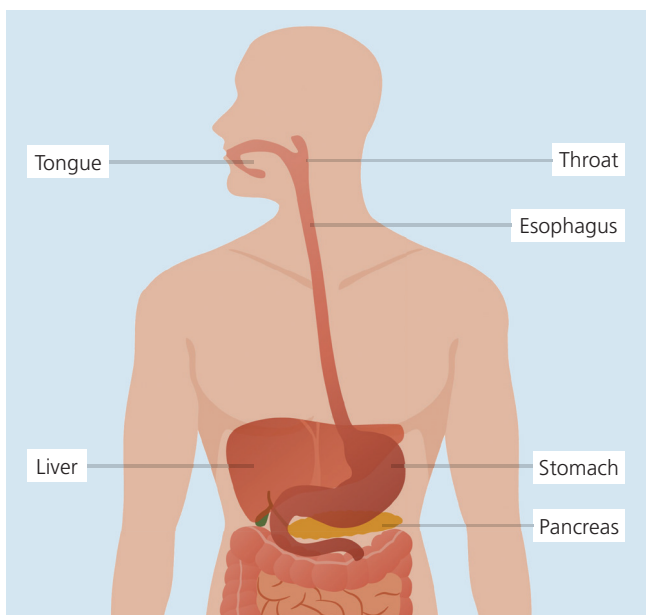


Fig. 1: The esophagus connects the mouth to the stomach

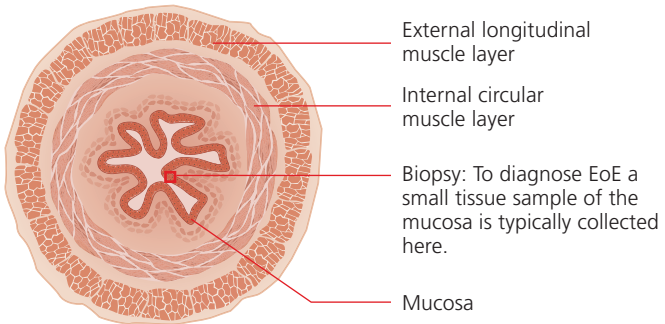


Fig. 2: Cross-section of the esophagus.

➤ What are the causes of EoE?

The esophagus is about 25 cm long with a diameter of about 2.5 cm, that normally stretches to 3.5 cm in diameter as a solid bolus passes through. It connects the oral cavity (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 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

- Mammalian milk
- Wheat
- 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”. Similar to asthma, airborne allergens are also suspected of potentially triggering EoE.



EoE is presumed to involve a chronic, inflammatory reaction triggered by 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. Yet, the connection between EoE and these disorders remains unclear. The exact causes and pathogenic processes of EoE are not completely understood and thus are the focus of current research.

In EoE inflammation involves many types of inflammatory cells, but the easiest to see are eosinophils. That inflammation makes the mucosa stiff and swollen, making the passage of solid foods difficult. In addition, over time, the inflammation causes fibrosis which hardens or stiffens the tissues so that they fail to stretch when solid food is swallowed, and the food gets stuck.

➤ **What are the symptoms of EoE?**

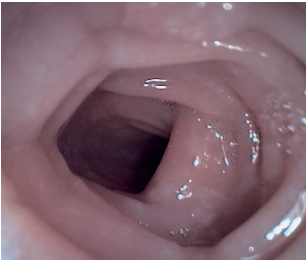
The main symptoms of EoE in adults include difficulty swallowing (so-called “dysphagia”) and/or pain during swallowing, also known as “odynophagia”, chest pain, and heartburn. In a worst-case scenario, EoE can even result in a prolonged obstruction of the esophagus, a so-called food bolus impaction. In this circumstance a bite of food gets stuck on its way through the esophagus (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.



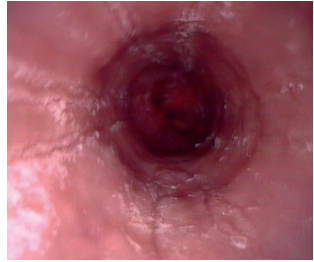
Normal



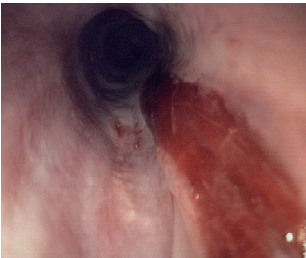
Inflammation: white deposits



Strictures (narrowing) with typical ring formation



Acutely inflamed EoE with lengthwise reddish furrows



Mucosal tear following successful dilation



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

Fig. 3: Endoscopic findings in the esophagus. In about 10%–25% of EoE patients, the esophageal mucosa 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.

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 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.
- Plentiful drinking in order to minimize or prevent difficulty 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 solid foods (see Figure 4). But it is also possible that the disease suddenly manifests even though a person never experienced difficulty swallowing when a piece of food becomes stuck in the esophagus.

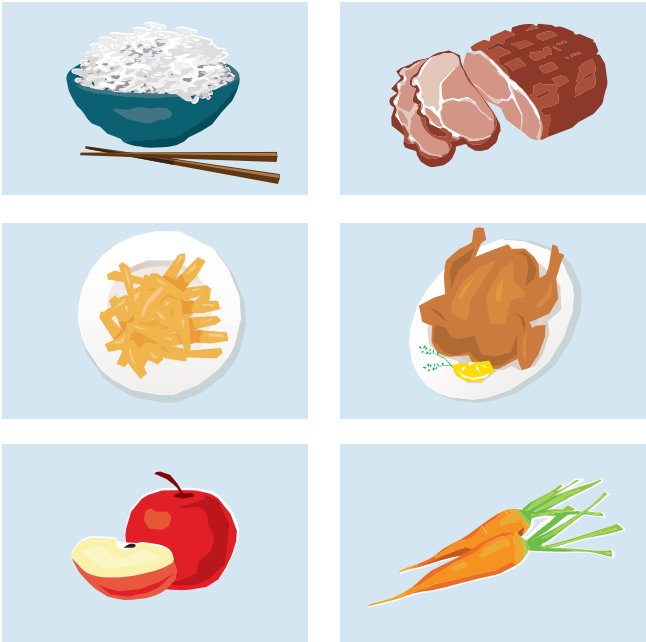


Fig. 4: Typical foods that cause difficulty swallowing include dry rice, meat, raw fruits and vegetables (e.g. carrots, apples) or French fries. Patients experience difficulty swallowing because these foods are very solid, not because they trigger acute allergies.

➤ How can EoE be diagnosed?

EoE can only be definitively diagnosed by a gastroenterologist. In addition to recognizing 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).

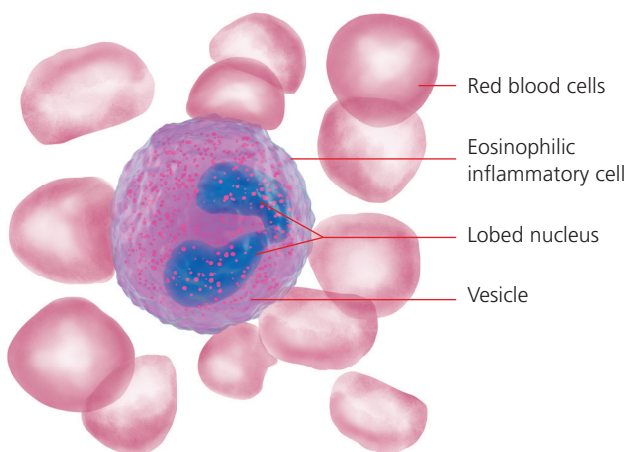


Fig. 5: An eosinophil (specialized white blood cell) surrounded by red blood cells. Inside the cell is a lobed nucleus (compartment where genetic material is stored) and numerous vesicles (small bubbles or granules) containing various inflammatory substances. Every human has small numbers of eosinophilic 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 but has emerged over the past two decades to a major cause of upper gastrointestinal morbidity. World-wide around 34–40 out of 100,000 inhabitants suffer from EoE, although there are large geographic variations. In many countries there is a rapid increase in the frequency of this condition.

➤ What are the risk factors for EoE?

The majority of patients with EoE are male (approx. 60–80%). 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.

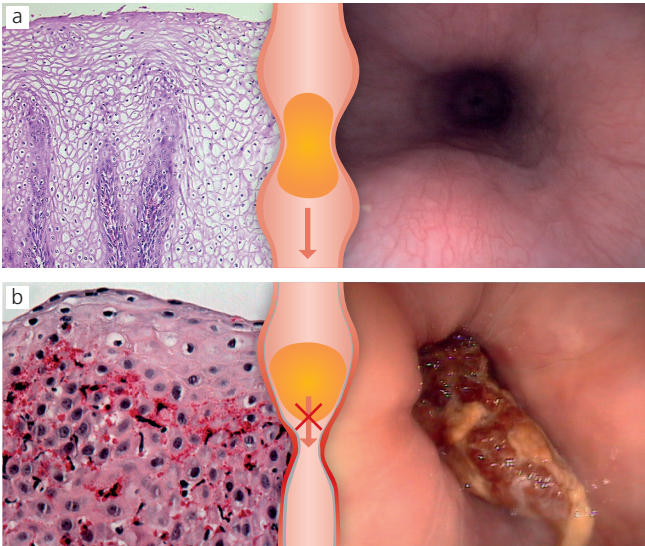


Fig. 6: a) Normal esophagus with no eosinophils
b) Increased eosinophils in an EoE patient

➤ How does EoE progress if left untreated?

If left untreated, the persistent inflammation caused by the presence of eosinophilic cells, over the years can result in scarring and subsequent narrowing of the esophagus (see Figure 6). Accordingly, 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 recommended: The first one is medication, usually in form of locally acting steroid products, which reduce the inflammation, or alternatively with proton pump inhibitors. The latter are usually used to inhibit the secretion of gastric acid, but acid is rarely a cause of EoE. Sometimes proton pump inhibitors can partly suppress the inflammation by a direct action but this is usually only a partial inhibition. Regulatory authorities in Europe and the USA have approved an immunomodulatory treatment for adults and children above 12 years of age who are inadequately controlled by conventional treatment, cannot tolerate it or for whom it is not an option. Country-specific regulations might apply. The second option involves special diets that avoid certain food allergens. The third option is dilation of the esophagus with 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 which is associated with prolonged untreated inflammation.

➤ Advanced disease

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

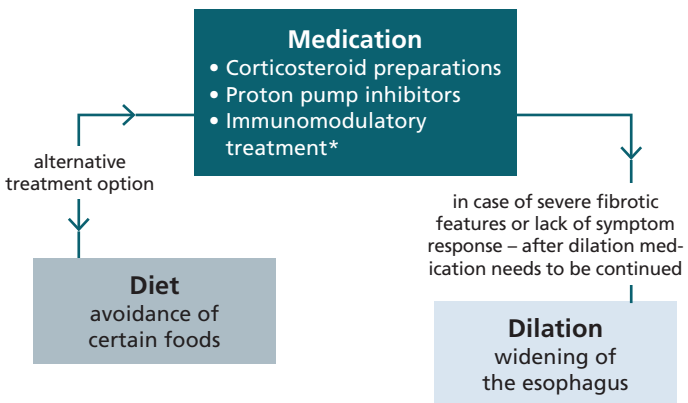


The different treatment options are applied based on the clinical picture: Medications and diets in the case of acute inflammation, dilation in the advanced stage once the esophagus has already narrowed.

➤ Long-term treatment is required

Currently, EoE cannot be cured with medications or diets. 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 accompanied by symptoms. It is possible to have esophageal inflammation without ever noticing anything. Therefore, an endoscopic follow-up examination of the esophagus should take place approx. 6–12 weeks following the start of treatment to verify therapeutic success.



**approved in Europe for EoE patients of at least 12 years of age with a least 40 kg body weight who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy*

DIFFERENT THERAPEUTIC OPTIONS

> MEDICATIONS

Local steroid treatment of the esophagus

Efficacy:

Local acting steroid drugs work directly on the lining of the esophagus and block several stages of the inflammatory process. They are usually well tolerated because they are rapidly inactivated in the liver and only a tiny fraction of steroid actually gets to other parts of the body via the bloodstream.



In clinical studies, of patients experience a reduction of inflammation and improvement of symptoms after 12 weeks of treatment.

Administration:

EoE used to be commonly treated with asthma sprays containing budesonide or similar active ingredients that were swallowed instead of being inhaled. But because these medications were developed to treat the respiratory tract, they are not ideal for coating the esophagus. Drugs with a specific technical formulation to improve adherence and delay absorption were developed to coat the esophagus for a more efficient treatment of EoE.

Side effects:

Locally acting steroid drugs are considered to be relatively safe. The most common side effect (< 10%) is a mild, local fungal infection called candidiasis. This infection can usually be treated easily with a local antifungal medicine without needing to stop taking the local steroid drug. Wider side effects of systemic steroids have not been seen with approved local steroid treatment options for EoE in over 250 k treatments.

Treatment duration:

The initial treatment phase with said products typically lasts 6 weeks, which can be extended to 12 weeks for patients who do not respond at first. After the initial phase a long-term treatment is recommended to keep EoE in remission.

Proton-pump inhibitors (PPIs)**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.

A study on PPI efficacy published in 2020 could show histological remission (defined as < 15 eosinophils per high-power field) in 48.8% of patients and clinical improvement (defined as a decrease of $\geq 50\%$ in dysphagia symptom score) in 71.0% of patients. Full clinical remission is seen in approx. 40%.

Administration:

Double standard therapeutic doses of proton pump inhibitors (PPIs) are used to treat 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 the doctor. If the patient does not experience any improvement, then other treatment strategies, such as treatment with local acting steroid drugs or diet, must be considered.

Effectiveness rates of PPI induction therapy depended on the PPI dosages prescribed. Histological remission rate and symptomatic improvement was higher for patients treated with high doses (defined as double dosage or higher) compared to standard or low doses. Standard doses of PPI included omeprazole 20 mg, pantoprazole 40 mg, esomeprazole 20 mg, lansoprazole 30 mg and rabeprazole 20 mg daily. The likelihood of achieving clinico-histological remission was greater for high compared to standard or low PPI doses (50.8% vs 35.8%, respectively; $P = 0.027$; $OR = 1.85$).

Immunomodulatory treatment

Efficacy

Dupilumab is a monoclonal antibody blocking two key cellular communication factors that drive EoE (interleukin 4 and interleukin 13). Dupilumab is approved in Europe for EoE patients of at least 12 years of age with a least 40 kg body weight who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.

Clinical studies showed that weekly treatment with subcutaneous dupilumab improved histologic outcomes and alleviated symptoms of EoE in both adults and adolescents in 60% after 24 weeks of treatment. Monoclonal antibody therapies may be very effective at reducing eosinophils without having much effect on the other aspects of inflammation from mast cells, lymphocytes and fibroblasts.

Side effects

The most frequently reported adverse events that occurred in the clinical EoE trials were injection-site reactions, upper respiratory tract infections and arthralgia.

Conjunctivitis and oral herpes occurred predominantly in atopic dermatitis studies.

Treatment duration

Duration of treatment is expected to be lifelong, but for EoE there is no long-term data available yet.

> 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, soya, 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. Elimination diets can be effective treatments for EoE, but pose psychosocial and financial challenges to patients and consequently may impair quality of life.

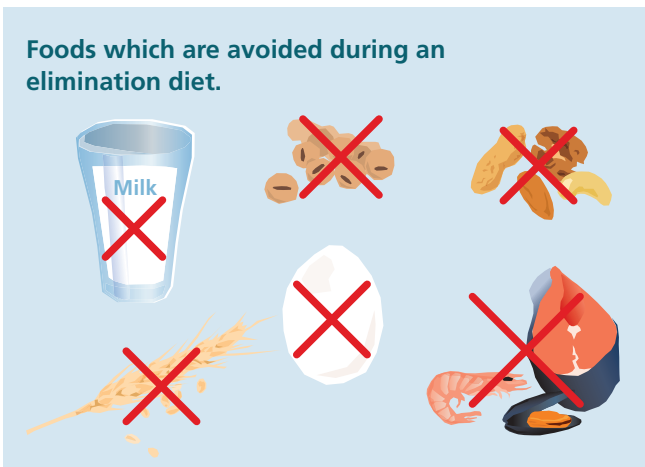


Fig. 7: Common food allergens

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. In EoE allergy tests are generally not specific, often misleading and are not recommended by the current guidelines.

Therefore, usually an empirical elimination diet is performed, which is based on excluding the two most common food triggers, milk and wheat, and stepping up to more exclusions if that is unsuccessful, or a more complex elimination of the 6 most common allergy-triggering foods with subsequent, controlled, stepwise reintroduction until the allergy-triggering “culprit” is identified. These diets have shown some effect in children and adults. Recent well controlled randomized studies show similar and relatively poor outcomes with either regime.

Procedure:

This diet involves the complete elimination of dairy products, wheat, eggs, soya, 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 (see Figure 8). In the best case, the inflammatory cells have then 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 wheat) are eliminated and if there is no response, then 4 or ultimately 6 foods are eliminated from the diet. This step-up approach can reduce the number of endoscopic inspections by about 20% on average.

Patients in whom the triggering foods are successfully identified should follow the diet over the long term (for months or years).



Although elimination diets help reduce symptoms for many patients, they need to be maintained for a long time.

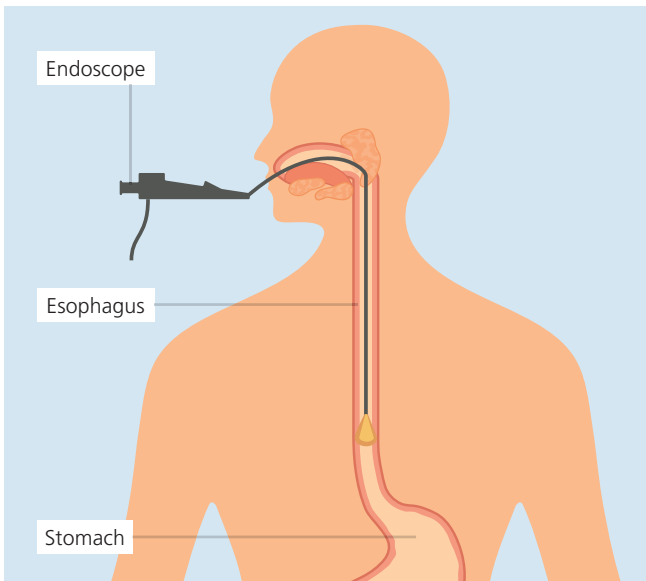


Fig. 8: Endoscopic examination of the esophagus

DILATION OF THE ESOPHAGUS

Efficacy:

About 75% of patients, treated by dilation, experience significantly improved symptoms that lasts up to 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 de-ploying 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).

In the case of failure of medication treatments, dilation therapy may help to stretch underlying fibrosis that is not responding to medication. In these cases usually no stricture is seen, but the whole esophagus should be dilated.

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 possibly must be repeated as new strictures form over time.

Side effects:

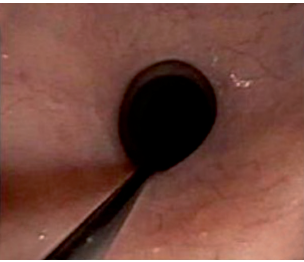
Pain during swallowing may occur in about half of the patients for 2–3 days following the procedure but this pain responds well to conventional pain relievers. The risk of complications, especially a hole (perforation) in the esophagus, is relatively low ($< 1\%$). A hole in the esophagus may be closed 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:

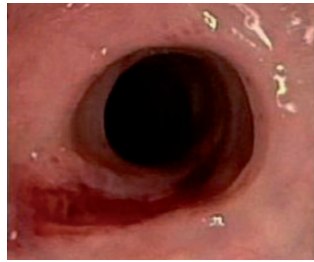
Dilations may be performed as often as necessary. Patients are usually required to undergo dilation treatment regularly if they are not additionally receiving anti-inflammatory treatment with medications or diets.



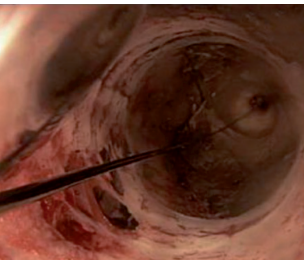
Dilation does not treat the causes of EoE, but instead merely involves the mechanical expansion of the constricted esophagus.



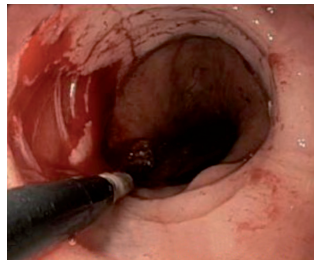
Stricture in the esophagus



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		
	Local steroid treatment of the oesophagus	Proton-pump inhibitors	Immunosuppressants
Reduces symptoms	+++	++	+
Reduces endoscopically visible inflammation	+++	++	+
Reduces microscopically visible inflammation	+++	++	+
Reduces stricture formation (narrowing) in the esophagus	+	—	Not known
Side effects	!	!	!
Limitations	—	Not approved for EoE**	High risk of side effects
Notes	Up to 85% of patients experience a reduction of inflammation and improvement of symptoms.	Effective in only a minority of EoE patients.	Good for preventing relapse, but with many side effects and high risk of infection.

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

	DIET		DILATION
Immuno-modulatory treatment	Elimination diet based on allergy testing	Empirical elimination diet ¹³	Dilation treatment of the esophagus
+	+	+	+
+	+	+	—
+	+	+	—
Not yet known*	—	—	+
	—	—	!
Higher costs	!	!	—
Good option for EoE patients who suffer from uncontrolled eosinophilic asthma or chronic rhinosinusitis with nasal polyps or severe neurodermitis.	None of the currently-available allergy tests predicts food triggers for EoE foods.	Roughly 30% chance that microscopically identifiable inflammation will be reduced. Multiple endoscopies of the esophagus required to identify the triggering food(s).	Dilation is recommended to be combined with a long-term anti-inflammatory therapy.

* No evidence yet for the effects of dupilumab on stricture resolution or stricture prevention

** No approved PPI therapy for the treatment of EoE

Fill out this symptom tracker if you notice your symptoms getting worse and you want to record and track them,

Think back over the past 7 days:	Date:	
Did you need to go to a doctor or the hospital because of difficulty swallowing?	☐ Yes ☐ No	
How many days did you have difficulty swallowing solid food?	☐ No difficulty swallowing ☐ On one day ☐ On more than one day ☐ Every day this week	
How painful was it to swallow solid food?	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 not painful very painful	
Did food ever get stuck in your throat while swallowing?	☐ Yes ☐ No	
What foods did you avoid because you thought they might get stuck?		
Did you cut any specific food into small pieces or put it in the blender to make it easier to swallow?	☐ Yes ☐ No	
Did it take you longer to eat than other people?	☐ Yes ☐ No	
How often did you eat together with friends or family?		
Which of these food groups did you leave out as part of an elimination diet?	☐ Dairy ☐ Wheat ☐ Soya and legumes ☐ Fish/shellfish ☐ _____ ☐ Nuts ☐ Eggs	
How are you currently treating your EoE?	☐ Topical Corticosteroids ☐ PPIs ☐ Elimination diet ☐ No treatment ☐ Other	
How does EoE impact your daily life?	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 no impact normal life not possible du to EoE	

or regularly to help you prepare for your routine check-ups with your doctor.

Date:	Date:
☐ Yes ☐ No	☐ Yes ☐ No
☐ No difficulty swallowing ☐ On one day ☐ On more than one day ☐ Every day this week	☐ No difficulty swallowing ☐ On one day ☐ On more than one day ☐ Every day this week
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 not painful very painful	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 not painful very painful
☐ Yes ☐ No	☐ Yes ☐ No
☐ Yes ☐ No	☐ Yes ☐ No
☐ Yes ☐ No	☐ Yes ☐ No
☐ Dairy ☐ Wheat ☐ Soya and legumes ☐ Fish/shellfish ☐ _____	☐ Dairy ☐ Wheat ☐ Soya and legumes ☐ Fish/shellfish ☐ _____
☐ Nuts ☐ Eggs	☐ Nuts ☐ Eggs
☐ Topical Corticosteroids ☐ PPIs ☐ Elimination diet ☐ No treatment ☐ Other	☐ Topical Corticosteroids ☐ PPIs ☐ Elimination diet ☐ No treatment ☐ Other
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 no impact normal life not possible du to EoE	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 no impact normal life not possible du to EoE

If you experience intense or recurring pain and problems swallowing, don't wait until your next appointment! Contact your gastroenterologist immediately.

NOTES



NOTES





Together we know more. Together we do more.

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