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S2k guideline Gastroesophageal reflux disease and eosinophilic esophagitis of the German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS)

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List of abbreviations

AGs	Working groups
APC	Argon Plasma Coagulation
APT	Atopy patch test
AWMF	Association of the Scientific Medical Societies e.V.
BDP	Federal Association of German Pathologists e.V.
CSACI	Canadian Society of Allergy and Clinical Immunology
DCCV	German Crohn's Disease/Ulcerative Colitis Association
DGAV	German Society for General and Visceral Surgery e.V.
DGKCH	German Society for Pediatric Surgery
DGP	German Society for Pathology e.V.
DGVS	German Society for Gastroenterology, Digestive and Metabolic Diseases
DSQ	Dysphagia Symptom Questionnaire
DTPA	Diethylene triamine pentaacetic acid
EndoFLIP	endoluminal functional lumen imaging probe
EoE	Eosinophilic esophagitis
EoEHSS	EoE specific histology score
ER	endoscopic resection
ERD	erosive reflux esophagitis
EREFS	Endoscopic Reference Score
ESGE	European Society of Gastrointestinal Endoscopy
EUREOS	European Consortium for Eosinophilic Disease of the GI Tract
6FED	6 Food Elimination Diet
FIRE	Food-induced immediate response of the esophagus
GERD	gastroesophageal reflux disease
GPGE	Society for Pediatric Gastroenterology and Nutrition e. V.
H -RA_2	H2 receptor antagonists
HE	Hematoxylin-eosin stain
HGD	High grade dysplasia
HPF	High Power Field
HRQOL	Health Related Quality of Life
CHD	coronary heart disease
LA degree	Los Angeles degree
LGD	Low grade dysplasia
LJ	Year of life
LPR	laryngo-pharyngeal reflux
NERD	non-erosive reflux disease
n.s.	not significant
NSAIDS	Non-steroidal anti-inflammatory drugs
ÖGD	Esophago-gastro-duodenoscopy
OIT	oral immunotherapy

PEES	Pediatric EoE Symptom Score
PPI	Proton pump inhibitors
RCT	randomized controlled trial
SAP	Symptom Association
SI	Symptom index
SSRI	Selective serotonin reuptake inhibitors
TR	time ratio
CNS	Central nervous system

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1 Guideline information

1.1 Publisher

1.1.1 Leading professional society

German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS)

1.1.2 Scope and purpose

Gastroesophageal reflux disease is one of the most common organic diseases of the upper abdomen. Although a class of acid inhibitors (proton pump inhibitors, PPI) has fundamentally improved the treatment of many patients since about 1990, a number of unresolved problems remain, such as the diagnostic and therapeutic approach to patients with unsatisfactory symptom control under PPI.
Furthermore, in addition to the annoying symptoms of reflux disease, some patients are at increased risk of developing cancer of the esophagus due to the development of mucosal remodeling in the esophagus (Barrett's esophagus)[1].

For the reasons mentioned above, the experts consider an update of the guideline to be particularly important. In addition, the guideline will be expanded to include the topic of eosinophilic esophagitis, now the second most common disease of the esophagus, for which there is no guideline in Germany to date.

1.2 Target orientation of the guideline

The goal of the guideline is to be easily applicable in family practice, internal medicine, surgery, pathology, pediatrics, and gastroenterology. In addition, the guideline is intended to provide a corridor of action for common decisions.
Patient target group e are patients* with gastroesophageal reflux disease or with eosinophilic esophagitis of any age.

1.3 Service area

Outpatient and inpatient, primary care, internal medicine, surgery, pathology, pediatrics and gastroenterology .

1.4 User target group/addressees

The guideline is addressed to gastroenterologists, surgeons, pathologists, patient representatives as well as affected persons and relatives and serves as information for internists, general practitioners, pediatricians and health care providers (health insurance companies, pension insurance companies).

1.5 Composition of the guideline group: participation of stakeholders

The guideline was developed by the German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS), which appointed Prof. Herbert Koop, Berlin, and Prof. Ahmed Madisch, Frankfurt, as coordinators. PD Dr. Petra Lynen Jansen and Pia Lorenz, DGVS office, Berlin, were methodologically responsible. Dr. Blödt, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF) , Berlin, provided methodological advice and moderated the consensus conference as a

neutral guideline expert. Torsten Karge was available for the guideline portal and provided technical support for the consensus conference.

The guideline project was advertised in the Journal of Gastroenterology and published on the AWMF website, so that other professional societies/representatives could register for participation. The relevant professional societies and patient groups were contacted and asked to nominate their representatives.

1.6 Representativeness of the guideline group: Participating professional societies

- German Society for General and Visceral Surgery (DGAV)
  F. A. Granderath (Mönchengladbach), J. Leers (Cologne)
- German Society for Pediatric Surgery (DGKCH)
  S. Hosie (Munich)
- German Society of Pathology (DGP)/Federal Association of German Pathologists (BDP)
  H. Bläker (Leipzig), R. Langer (Linz)
- Society for Pediatric Gastroenterology and Nutrition (GPGE)
  A. Hörning (Erlangen), A. Schmidt-Choudhury (Bochum), T. Wenzl (Aachen)

The German Society of General and Family Medicine (DEGAM) and the German Society of Internal Medicine (DGIM) were not involved in the preparation of the guideline.

1.7 Representativeness of the guideline group: Participation of patients *innen

G. Möller (Hanau) of the German Crohn's Disease/Ulcerative Colitis Association (DCCV)

Even if the DCCV has no thematic reference to the guideline, Ms. Möller will be involved as a patient representative of the DCCV, as she has a lot of experience in considering the perspective of patients.

In addition to the steering group (*Table 1*), five working groups (WGs) were formed, each of which was headed by a leader (*Table 2*). In addition to gastroenterologists, pediatricians, pathologists, internists and surgeons participated in the working groups.

Table 1: Steering group

Name	Location	Responsibility
H. Koop	Berlin	DGVS
A. Madisch	Frankfurt	DGVS
J. Labenz	Siegen	DGVS
J. Leers	Cologne	DGAV
S. Miehlke	Hamburg	DGVS
O. Pech	Regensburg	DGVS

Table 2: Members of the Guideline Group

WG 1: Reflux disease: epidemiology and diagnostics	WG Management	D. Schilling, Mannheim (DGVS)
	WG members	H. Allescher, Garmisch-Partenkirchen (DGVS) C. Pehl, Vilsbiburg (DGVS)
WG 2: Reflux disease: conservative therapy	WG Management	J. Labenz, Siegen (DGVS)
	WG members	A. Madisch, Frankfurt (DGVS) T. Wenzl, Aachen (GPGE)
WG 3: Reflux disease: surgical / endoscopic therapy	WG Management	J. Leers, Cologne (DGAV)
	WG members	K. Caca, Ludwigsburg (DGVS) T. Frieling, Krefeld (DGVS) F. A. Granderath, Mönchengladbach (DGAV) S. Hosie, Munich (DGKCH)
WG 4: Barrett's esophagus	WG Management	O. Pech, Regensburg (DGVS)
	WG members	H. Bläker, Leipzig (DGP/BDP) H. Messmann, Augsburg (DGVS)
WG 5: Eosinophilic esophagitis: diagnosis and therapy	WG Management	S. Miehlke, Hamburg (DGVS)
	WG members	A. Hörning, Erlangen (GPGE) H. Koop, Berlin (DGVS) R. Langer, Linz (DGP/BDP) C. Schlag, Munich (DGVS) A. Schmidt-Choudhury, Bochum (GPGE) U. von Arnim, Magdeburg (DGVS)
WG overlapping		G. Möller, Hanau (DCCV)
Coordinating		H. Koop, Berlin (DGVS) A. Madisch, Frankfurt (DGVS)

2 Methodological approach

2.1 Evidence Synthesis

2.1.1 Methodology basics

Literature research

The literature search was conducted individually in the individual working groups. The details of the search and selection are presented in the guideline report.

Scheme of recommendation grading

The strength of the recommendation results from the wording used (shall/should/could) according to the gradation in *Table 3*. The consensus strength was determined according to *Table 4* determined.

Table 3: Scheme for graduation of recommendations

Description	Syntax
strong recommendation	should
recommendation	should be
open	can

Table 4: Classification of consensus strength

Consensus	% Approval
strong consensus	≥ 95
consensus	≥ 75 - 95
majority approval	≥ 50 - 75
no majority approval	< 50

Recommendations that were taken over unchanged from the last guideline were marked with "reviewed 2022". Recommendations marked "modified 2022" have been modified compared to the previous 2014 version.

Statements

Statements are presentations or explanations of specific facts or issues without an immediate call to action. They are adopted in accordance with the procedure for recommendations as part of a formal consensus process and can be based either on study results or on expert opinions.

Decide wisely

Recommendations marked with "Decide Wisely" have been selected for the "Decide Wisely" initiative of the German Society of Internal Medicine. These recommendations are intended to provide concrete assistance in determining the indications for diagnostic and therapeutic measures in order to avoid underuse or overuse. For more information, visit https://www.klug-entscheiden.com/.

2.2 External appraisal and adoption

2.2.1 Adoption by the boards of the issuing professional societies/organizations

The complete guideline was reviewed and consented by the executive boards of all participating professional societies and was available as a consultation version for 4 weeks from September 08, 2022 to October 09, 2022 to the professional public for comment on the DGVS website and at the AWMF. Comments were solicited via the DGVS newsletter. All proposed changes are presented in the guideline report.

2.2.2 Editorial independence and Guideline funding

The preparation of the guideline was editorially independent. The DGVS did not exert any influence on the content. The DGVS financed the use of the guideline portal, the kickoff meeting including travel expenses, and the online consensus conference. There was no financial participation by third parties. Mandate holders and experts worked exclusively on a voluntary basis.

2.2.3 Disclosure of and handling of conflicts of interest

In accordance with the AWMF rules for dealing with conflicts of interest, all participants made their declarations on the corresponding AWMF form (Form 2018). Conflicts of interest were screened by the guideline coordinators and Ms Blödt (AWMF), categorized according to AWMF criteria as low, moderate, or high with respect to each recommendation, and subsequently presented to the guideline group before the start of the consensus conference, which conducted a joint assessment of the conflict of interest declarations .

Paid lecturing/or training and paid authorship/or co-authorship were considered minor conflicts of interest and had no consequences in terms of voting.

The following conflicts of interest were classified as moderate:

- Consultant or expert activity or paid participation in a scientific advisory board of a company in the health care industry (e.g. pharmaceutical industry, medical device industry), a commercially oriented contract institute or an insurance company
- Cooperation in a scientific advisory board (advisory board)
- Research projects/conduction of clinical studies: financial contributions (third-party funds) for research projects or direct financing of employees of the institution from a company in the health care industry, a commercially oriented contracting institute or an insurance company

The following companies were identified as having a potential conflict of interest: Falk (top. steroids), Reckitt Benckiser (alginates), Boston, Medtronic (Barrett's esophagus).

Owner interests (patent, copyright, ownership of business shares, stocks, funds with participation of healthcare companies) were classified as high conflicts of interest. High conflicts of interest related to the guideline were not identified.

As a result, seven experts were found to have moderate conflicts of interest. Moderate conflicts of interest resulted in abstention from voting, or double voting (1x without, 1x with the affected persons, anonymous voting) took place. However, there were no differences in the results of these votes, so that there was no deviation from the consensus in the vote with the abstentions.
In addition, the interdisciplinary, representative composition of the guideline group and the structured consensus-building under neutral moderation are rated as protective factors against bias.
All declarations of interest are presented in the guideline report.

2.3 Dissemination and implementation

2.3.1 Dissemination and implementation concept

The guideline is published in addition to the Journal of Gastroenterology at AMBOSS and on the homepages of the DGVS (www.dgvs.de) and the AWMF (www.awmf.de). An English abridged version of the guideline is also published in the Journal of Gastroenterology.

2.3.2 Validity period and updating procedure

The validity is five years (June 30, 2027). The revision will be initiated by the guideline officers of the DGVS. The steering group will review the need for updating the guideline on an annual basis. The DGVS office (leitlinien@dgvs.de) is available as a contact person.

2.4 Editorial note

2.4.1 Participatory decision making

All recommendations of the guideline are to be understood as recommendations that are made and implemented in the sense of a participatory decision-making process between physicians and patients and, if applicable, their relatives.

2.4.2 Special note

Medicine is subject to a continuous development process, so that all information, in particular on diagnostic and therapeutic procedures, can only correspond to the state of knowledge at the time of printing of the guideline. The greatest possible care has been taken with regard to the recommendations given for therapy and the selection and dosage of medications. Nevertheless, users are urged to consult the manufacturers' package inserts and expert information for verification and, in case of doubt, to consult a specialist. In the general interest, any discrepancies should be reported to the DGVS. The user himself remains responsible for any diagnostic and therapeutic application, medication and dosage. In this guideline, registered trademarks (protected trade names) are not specially marked. It can therefore not be concluded from the absence of a corresponding reference that it is a free trade name. The work is protected by copyright in all its parts. Any use outside the provisions of copyright law without the written consent of DGVS is prohibited and punishable by law. No part of the work may be reproduced in any form without written permission. This applies in particular to reproductions, translations, microfilming and the storage, use and exploitation in electronic systems, intranets and the Internet.

1 Guideline - Epidemiology and diagnostics

Statement 1.1 (new 2022)

GERD is present when there are bothersome symptoms and/or lesions in the esophagus due to reflux of stomach contents into the esophagus**.**

[Strong consensus]

Comment:

The Montreal Classification (*Figure 1*) provides the first generally applicable and authoritative nosological definition of gastroesophageal reflux disease (GERD) : GERD develops when reflux of gastric contents causes bothersome symptoms and/or complications [2]. It includes the pathophysiologic process of gastroesophageal reflux as well as a symptom-based definition for clinical application of the definition. "Disturbing symptoms and/or complications" allows sufficient variability in assessing the degree to which patients find the symptoms or consequences of GERD to be disabling. Even asymptomatic patients with a GERD complication (e.g., Barrett's esophagus) are covered by the Montreal classification. The definition is independent of specific measurement methods and captures patients by symptomatology alone. On the other hand, it also classifies GERD - regardless of the presence of clinical symptoms - based solely on technical evidence of reflux (pH-metry, impedance-pH-metry) or evidence of reflux sequelae (endoscopy, histology, electron microscopy) and symptoms. Finally, the Montreal classification does not specify whether the reflux must be acidic, weakly acidic, basic, or gaseous. The Montreal classification has been validated by various expert groups and has been adopted by other gastroenterological societies.

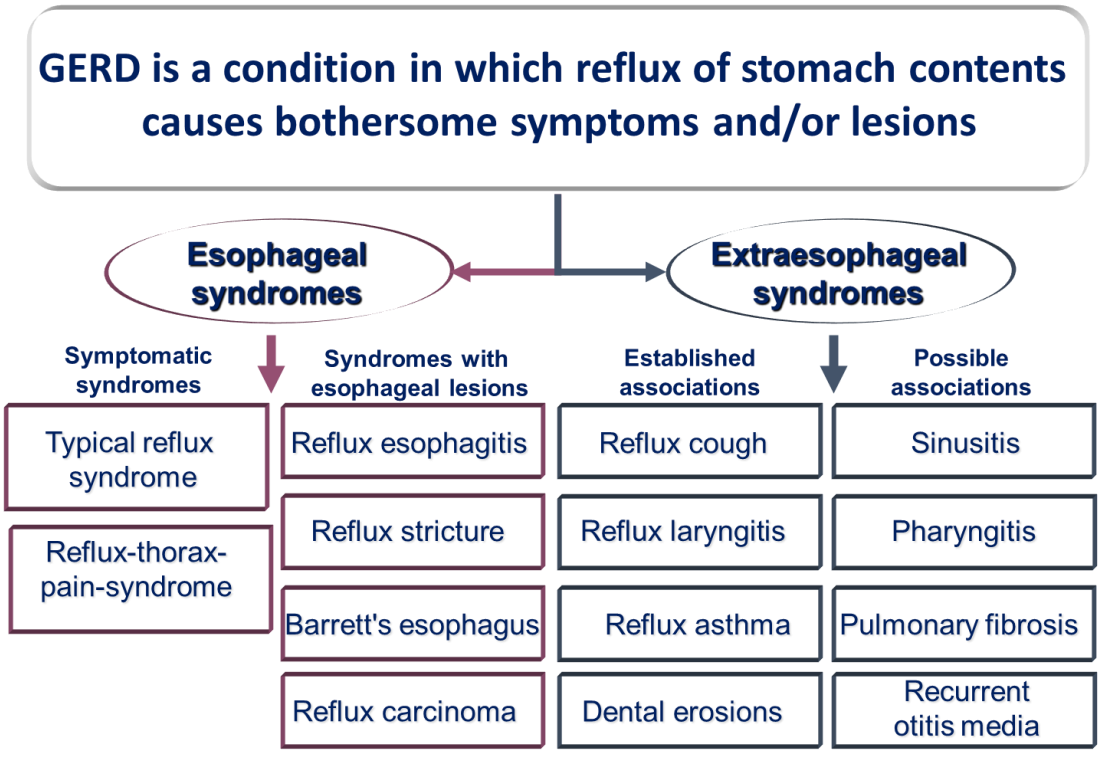


Figure 1: Montreal classification (consensus)

The term GERD subsumes:

- erosive reflux esophagitis (ERD)
  Detection of inflammatory changes of various severities including peptic stenosis.
- non-erosive reflux disease (NERD)
  typical reflux symptoms affecting quality of life without evidence of endoscopic lesions
- thoracic pain
  GERD as a major cause of noncardiac chest pain (without concomitant esophageal symptoms)
- hypersensitive esophagus
  Reflux quantitatively within normal range, but high association of reflux episodes and symptoms (compared with functional heartburn, which lacks this association); given scientific data since 2006, more precise concepts now exist
- extraesophageal manifestations
  Symptoms in extraesophageal organs (oral cavity, lungs); it is only an association without proving causal relationship. Solitary symptoms (cough, laryngitis, asthma, etc.) as the sole manifestation are rare. Many other postulated extraesophageal manifestations (dental erosions, otitis media, halitosis, etc.) are further without substantiated evidence
- Complications of GERD: V. a. bleeding and stenosis
- Barrett's esophagus
  Intestinal-type metaplasia of the distal esophagus with potential progression to dysplasia and carcinoma

The Montréal Classification is a priori not designed as a diagnostic guideline, even though appropriate diagnostic references have been given in individual points.

The prevalence of GERD is increasing in recent years and it is higher in the countries with high standard of living with 15-25% than in the poorer countries with 10% [3, 4]. Established risk factors for the development of GERD are increased body mass index, nicotine abuse, and genetic predisposition [5] as well as hiatal hernia [6] Infection with *Helicobacer plyori* seems to reduce the risk [7].
GERD negatively affects quality of life, prevalence and permanent need for therapy consumes high financial and human resources in the healthcare system [8].
However, a population-based study (HUNT study) demonstrated that GERD does not increase all-cause mortality or Barrett's carcinoma risk compared with the normal population. A cohort of 4758 GERD patients was compared with the population of 51,381 people [9].

Statement 1.2 (new 2022)
There is no gold standard for the diagnosis of GERD. Exclusive evidence for the diagnosis of GERD is present if there is an erosive reflux lesion LA C or D or a Barrett's esophagus (histologically > 1 cm) or a peptic stenosis or pathological pH-metry with an acid exposure time > 6% in the diagnosis.

[Strong consensus]

Comment:

There is no singular procedure that alone can prove or exclude reflux disease. This is true for anamnestic data as well as for endoscopic-histological or functional diagnostic examinations (pH-metry or impedance-pH-metry). The accuracy of a medical history taken by an experienced gastroenterologist, for example, is only 70% sensitive and 67% specific, as the Diamond study was able to show very impressively [10]. Discrepancies between the expression of patients and the resulting perception and interpretation by physicians can play a significant role (heading).

This lack of a diagnostic gold standard has led to the development of criteria by which reflux disease can be classified as very likely or very unlikely. Naturally, there is also a considerable gray area here in which a clear classification is not possible.

Table 5: Modified according to Lyon Consensus [11]

	Endoscopy	pH/ pH impedance measurement	High Resolution Manometry
Conclusive evidence for pathological reflux	LA C and D esophagitis Barrett esophagus Peptic stricture	Acid exposure > 6 %	
Marginal evidence or inconclusive evidence.	LA A or LA B Esophagitis	Acid exposure 4-6 % 40 - 80 reflux episodes	
Supplementary parameters *(which can be confirmation in both directions by presence or absence).*	Histology Electron microscopy Low mucosal impedance	Reflux- symptom association >80 reflux episodes Low nocturnal basal impedance Low conclusion induced peristaltic wave	Hypotensive esophagic cardiac junction Hiatal hernia Esophageal hypomotility
Evidence against the presence of GERD		Acid exposure <4 % <40 reflux episodes	

The Lyon Consensus (*Table 5*). This is based on both endoscopic and functional diagnostic findings. The findings listed in *Table 5* listed criteria for or against evidence for the presence of GERD have recently been validated in a bicentric study and have been added to the table [12]. Healthy volunteers as well as patients with ERD and NERD were examined by means of wireless long-term pH metrie under PPI pause (96 h measurement time). The data show that the mean acid exposure time < 4 % seems to be physiological, but it also shows that the conclusive evidence for GERD is rather at an acid exposure time of 7 %; restrictively, it must be pointed out that there are no standard values and considerable

variability from day to day in such long-term pH measurements. In contrast to the Lyon Consensus postulation of definite evidence for GERD only from an LA C situation, the data already show that LA B-D supports the diagnosis of GERD. However, the validation of the Lyon Consensus was performed on a still small collective, insofar further studies are needed. Whether manometric findings can be used to increase the discriminatory power of the diagnosis also needs to be confirmed. On the other hand, general clinical experience suggests that GERD is not present in the absence of reflux esophagitis and simultaneous lack of improvement during therapy with 2 x 40 mg esomeprazole (currently the most effective PPI).

There are currently no valid diagnostic criteria for evaluating endoscopic and/or functional diagnostic findings with respect to a reliable diagnosis of extraesophageal manifestations of GERD.

Statement 1.3 (new 2022)

Response to PPI has no relevance in confirming the diagnosis of GERD.

[Strong consensus]

Comment:

Because of good therapeutic results in some reflux patients, it seemed reasonable to draw diagnostic conclusions from symptomatic response to PPI therapy. However, 69% of patients with ERD, 49% with ERD, and as many as 35% without pH-metric or endoscopic evidence for the presence of GERD showed a symptomatic response to PPI therapy [13]. Sensitivity and specificity of the "PPI test" for typical symptoms are 71 and 44 %, respectively. The PPI test is an unsuitable diagnostic method in that it has a low sensitivity for ERD/NERD and also a specificity that is too low at 60% and therefore also responds in patients with functional dyspepsia [14].

Work with pH metrie and impedance measurement has shown that only half of the actual reflux episodes were detected with pH metrie alone [15]. Further data highlight that 28% of all reflux associated symptoms are due to non-acid reflux. Thus, understandably, PPI response correlates with reflux symptoms only when the cause is actually acid reflux [16]. This once again justifies the uselessness of the PPI test.

Recommendation 1.4 (new 2022)

For medical reasons, further (e.g., endoscopic) clarification can be performed early and primarily, i.e., instead of empirical therapy.

[Recommendation open, strong consensus]

Comment:

In a multicenter study of patients with typical reflux symptoms comparing probationary PPI therapy with esomeprazole with primary endoscopy, both approaches were equally effective. Primary drug therapy was more cost-effective, saving 86-90% of endoscopies [17].

In GERD patients, 70% of endoscopies are unremarkable [18]. If patients are pretreated at the time of index endoscopy, this proportion of endoscopies with mucosal lesions is reduced to 10% [19]. Thus, the management of the disease is changed in the fewest cases. Overlooking relevant other findings is rare: in 73,335 patients with suspected uncomplicated reflux disease, esophageal tumors were found in 0.1% of these examinations, gastric tumors in 0.1%, strictures in 2.8%, and higher-grade esophagitis in 2%. 5.6% of those examined had Barrett's esophagus [20].

Therefore, if there is much to be said for primary therapy in the absence of alarm symptoms, endoscopy naturally provides some prognostically important information before therapy is initiated (e.g., higher-grade reflux esophagitis). In addition, endoscopy may help to reassure frightened patients, as studies in patients with functional dyspepsia have shown [21]. In this respect, the indication for endoscopy should be given generously if the patient wishes it (or if the classification of the symptoms is uncertain).

Recommendation 1.5 (modified 2022)
If alarm symptoms are present or if probationary therapy is primarily unsuccessful, further clarification should be performed by means of an ÖGD.

[Strong recommendation, consensus]

Comment:
Immediate endoscopy is always indicated if alarm symptoms are present. Alarm symptoms include:

- Dysphagia
- Odynophagia
- Evidence of gastrointestinal hemorrhage (including iron deficiency anemia).
- Anorexia
- Unwanted weight loss
- Recurrent vomiting
- Familial history for gastrointestinal tumors

Even in the case of symptoms that are primarily interpreted as GERD symptoms and do not improve with PPI therapy, it is obligatory to perform an OED. The aim is to find prognostically important differential diagnoses (e.g. eosinophilic esophagitis, achalasia) and to diagnose complications of GERD (peptic stenosis, Barrett's esophagus, Barrett's carcinoma). The need for endoscopic workup of refractory patients is supported by the fact that relevant findings are raised in 49 [19].

Recommendation 1.6 (modified 2022)
If reflux symptoms have been present for several years, an EGD should be performed to detect Barrett's esophagus.

[Recommendation, strong consensus]

Comment:

Risk factors for the presence of Barrett's esophagus are well defined. A meta-analysis of 20 studies and a total of 74943 patients with Barrett's esophagus identified age, male sex, nicotine abuse, central obesity, and length of Barrett's esophagus as major risk factors for developing adeno-carcinoma [22]. Nevertheless, Barrett's esophagus has been previously diagnosed in only 5% of cases with Barrett's carcinoma [23].

To minimize this deficit, a "once-in-a-lifetime" endoscopy in chronic reflux patients is useful to detect or exclude Barrett's esophagus. The main focus is on those patients who already have dysplasia. There is no evidence for an endoscopic selection based on symptoms, since 40% of carcinoma patients do not have a high symptom burden [24]. Systematic screening programs seem to be useful, because according to a systematic analysis of retrospective case control studies the diagnosis of dysplastic/malignant changes in Barrett's esophagus can be made earlier and mortality can be reduced [23]. Nevertheless, a general population-based screening cannot be recommended due to lack of data [25].

Recommendation 1.7 (modified 2022)

If symptoms are compatible with reflux disease and evidence of erosive reflux esophagitis, no further diagnosis should be made if therapy is successful.

[Recommendation, strong consensus]

Comment:

Although low-grade reflux esophagitis, such as esophagitis of LA grade A [18, 19] often an incidental finding and therefore not proving the presence of reflux disease, this in combination with typical reflux symptoms clearly supports the diagnosis. While the Lyon Consensus [11] defines LA C reflux esophagitis and D esophagitis as conclusive for the presence of GERD, there is usually little doubt about the diagnosis in the presence of typical reflux symptoms and an LA grade B [12]. Supplementary examinations (e.g., impedance pH-metry) are thus unnecessary.

Recommendation 1.8 (modified 2022)

Endoscopic classification of reflux esophagitis should be according to the Los Angeles classification.

[Strong recommendation, strong consensus]

Comment:

In contrast to other endoscopic classifications (Savary-Miller, MUSE), the Los Angeles classification has been [26] is now substantially validated and should be applied in the graduation of esophageal lesions today. It correlates with results of functional diagnostic studies [26]and therefore the Lyon consensus also refers to this classification [11]. Therefore, other classifications should no longer be used.

Statement 1.9 (new 2022)

Esophageal biopsies are inappropriate for the diagnosis of NERD.

[Strong consensus]

Comment:

Histologic hallmarks of esophageal mucosal damage due to pathologic reflux have been identified as basal cell hyperplasia, papilla elongation, intraepithelial eosinophils, neutrophils, and mononuclear cells, necrosis, erosions, healed erosions, and widening of intercellular clefts [27, 28], some of which result in endoscopically visible lesions. Histologic criteria have not always been found to be reproducible in further studies [29], as none of the features is pathognomonic. In controlled series using conventional forceps biopsies and blinding the examiner, patients with confirmed NERD could not be distinguished from nonreflux patients beyond reasonable doubt [30]. Only with an elaborate structured histopathological protocol, the biopsy can possibly contribute to the diagnosis [31, 32]. The significance of histology for the diagnosis of eosinophilic esophagitis is unaffected.

Recommendation 1.10 (modified 2022)

In cases of PPI refractory typical symptoms, dysphagia, and/or endoscopic suspicion of eosinophilic esophagitis (EoE), at least 6 biopsies should be obtained from several levels of the esophagus, especially from regions with endoscopic abnormalities (see recommendation 5.9).

[Recommendation, strong consensus]

Comment:

Eosinophilic esophagitis (EoE) may manifest alone under the clinical presentation of heartburn [33]. In this respect, EoE must always be considered in the differential diagnosis of reflux disease, and this is especially true for refractory cases. Since even in knowledge of subtle changes (EREFS classification) may well lack typical morphological changes for EoE, bioptic diagnosis should always be performed in refractory cases. Accordingly, a sufficient number of biopsies at different heights including the proximal esophagus should be performed.

Recommendation 1.11 (new 2022)

In patients with presumed typical reflux symptoms but PPI refractory symptoms, a combined pH metric/impedance measurement should be performed without or with continued PPI medication, depending on the question, to differentiate persistent acid or nonacid reflux, hypersensitive esophagus, or nonreflux-related symptoms.

[Recommendation, strong consensus]

Comment:

In the clarification of therapy-refractory complaints, it depends in each individual case on the question on which the examination is based: is it a fundamental clarification of the (also acid-induced) reflux or is it a clarification of the therapy effect under ongoing PPI therapy.

The fact that up to 35% of patients with persistent reflux symptoms on PPI have inadequate suppression of acidic (pH< 4) gastroesophageal reflux suggests that PPI therapy should be measured [34, 35]. These patients can be diagnosed by impedance pH-metry under PPI therapy. More often, however, the cause of persistent symptoms is the lack of suppression of weakly acidic (pH between 4 and 7) or nonacidic volume reflux [36, 37]. In patients with refractory symptoms, 24-hour impedance pH measurement under PPI can be used to indicate dose escalation or de-escalation [38]. Furthermore, impedance pH-metry can be used to differentiate patients with hypersensitive esophagus (normal acid exposure, but positive symptom association) or with functional heartburn (normal acid exposure, no symptom association) [39]. Thus, patients with hypersensitive esophagus had a higher proportion of weakly acidic reflux ("weakly acidic reflux") and of proximal reflux episodes [40, 41]. Acid reflux (number of episodes, volume) and decreased acid clearance were mainly associated with erosive changes, whereas weakly acidic reflux episodes were less associated with erosive changes than with symptom development in NERD patients [42]. Patients identified as having a hypersensitive esophagus by impedance-pH metrie can be directed to therapy other than PPI that is much more effective [43]. Selective serotonin reuptake inhibitors (SSRI - fluoxetine in this study) are more effective than PPI in symptom reduction in hypersensitivity in contrast to patients with persistently elevated acid reflux [44].

In some cases, however, it is a matter of basic proof of pathological acid reflux, e.g., in the preoperative workup. In these cases, impedance pH-metry without PPI is indicated.

Recommendation 1.12 (new 2022)

In the diagnostic context of reflux disease, high-resolution manometry should be performed in:

1. Non-conclusive diagnosis of GERD for differential exclusion of motility disorder.
2. Before surgical treatment of GERD

*s. Recommendation 3.2 and Recommendation 3.3.

[Recommendation, strong consensus]

Comment:

The significance of the diagnostic procedure, which is now accepted only as high-resolution (HR) esophageal manometry, has not yet been adequately defined. There is no doubt that manometry should be performed prior to antireflux surgery. If impedance pH-metry does not yield a conclusive result, manometry can provide additional information (e.g., by revealing hypomotile disorders of esophageal motility) [45, 46]. HR esophageal manometry also has diagnostic value in PPI-refractory heartburn and inconclusive findings on endoscopy and pH-metry impedance measurement. Yadlapati [47] was able to show that prolonged HR manometry over 90 minutes after a "refluxogenic" meal detected supragastric regurgitation as the cause of discomfort in 42% of patients and rumination syndrome in 20% of patients. The combination of HR pressure measurement with impedance measurement is particularly suitable for the detection of these diagnoses.

Recommendation 1.13 (new 2022)

Laryngopharyngeal pH metry alone should not be used to evaluate for laryngopharyngeal symptoms.

[Recommendation, strong consensus]

Comment:

Globus sensation, clearing of the throat, hoarseness and dry cough are very distressing symptoms, which are often wrongly attributed causally to reflux disease. These symptoms are accompanied by a considerable restriction of the quality of life and at the same time the diagnostic and therapeutic possibilities are limited [48]. Laryngopharyngeal reflux as a variant of extraesophageal reflux is often blamed as the cause of such symptoms, however, there is no sufficient pathophysiological evidence for such a reflux sequence, and therapy studies with high-dose PPI do not show clear results either [49].

The Restech pH Catheter is intended to measure pH in liquid and aerosol reflux as a nasopharyngeal measurement system. There is no clear evidence that the measured data of acidic or alkaline reflux are pathophysiologically responsible for the complaints. Whether this is also true for patients who show clear evidence of GERD in the 24-h impedance pH measurement (should be applied uniformly throughout the manuscript) is still unclear. The Restech procedure is also not predictive of the success of probational PPI therapy or even a surgical procedure for occlusive GERD.

Recommendation 1.14 (new 2022)

Radiologic studies should not be used for primary diagnosis of GERD.

[Strong recommendation, strong consensus]

Comment:

Gastroesophageal reflux can be detected on single and double contrast examination of the esophagus or esophagus and stomach [50-52]. However, due to spontaneous physiological reflux during the examination, the sensitivity of radiological methods is only about 35% compared to pH-metry [53]. This sensitivity can be increased up to 70-80% by additional provocation such as coughing, Valsalva maneuver, positioning (e.g. oblique right rotation in supine position) as well as the so-called wet siphon test [54, 55]. However, the increase in sensitivity due to the provocation maneuvers is at the cost of a decrease in specificity, which reaches a maximum of 74%. At best, radiological examinations may be useful for a surgical pre- and postoperative morphological assessment in anti-reflux surgery.

Nuclear Medicine

Esophageal scintigraphy with the nonabsorbable radiopharmaceuticals 99mTc-tin colloid, 99mTc-sulfur colloid, or 99mTc- diethylene-triamine-pentaacetic acid (DTPA) is well established for the diagnosis of esophageal motility disorders [56]), but can also be used to diagnose (postprandial) reflux [57-61]. Compared with the results of 24-hour pH-metry, sensitivities of 48-90% and specificities of 76%-100% are reported for esophageal scintigraphy [62-66]. The advantage of esophageal scintigraphy is its lack of invasiveness. Compared to radiological reflux diagnostics, esophageal scintigraphy is characterized by significantly lower radiation exposure, quantifiability of reflux, and better sensitivity and specificity [64]. In addition, late scintigraphic images can be used to search for pulmonary aspiration [66]Recent studies with digital reflux

scintigraphy seem to have potential in the diagnosis of laryngopharyngeal reflux. Here, there are correlation studies with 24 h impedance pH metrie showing that this method is significantly more sensitive than impedance measurement [67].

2 Guideline - Drug therapy

2.1 Definitions

Acute therapy: any treatment at initial diagnosis/first presentation or exacerbation of known GERD.
Long-term therapy: any treatment after completion of acute therapy.

- Continuous long-term therapy: regular intake of a drug (e.g. also intake every 2nd day).
- Intermittent therapy: repetition of an acute therapy (s.d.) as needed.
- Demand therapy ("on demand"): Taking a drug only when symptoms occur or at / before situations that typically cause symptoms, with limitation of the maximum amount of the drug per day (e.g., max. 1x per day).

2.2 Therapy goals

Symptom Control

Reflux symptoms that are perceived as bothersome are the reason for medical consultation in the vast majority of patients. Accordingly, satisfactory control of symptoms, regardless of the type of manifestation, is an important therapeutic goal in patients with GERD [68, 69]. Inadequate symptomatic response is associated with reduced quality of life in physical and psychological terms [8]. Complete symptom freedom is often not achieved, especially in clinical practice outside of trials [70]. There are few data on the question of when satisfactory symptom control is achieved from the patient's perspective with residual symptoms . In a post hoc analysis of treatment trials, patients with NERD were satisfied when mild reflux symptoms occurred no more frequently than once per week [71]. It must be considered in this question that patients react in psychological and physical respect quite differently to a reflux disease or are affected by such a disease and can have thereby quite different requirements to the management or the therapy goals [72].

Healing reflux esophagitis

The healing of endoscopically visible reflux lesions (erosions, ulcerations, mucosal breaks) in the Los Angeles classification is usually the primary goal of therapy studies. These have shown that in the case of full-dose PPI therapy over 4 weeks (Los Angeles A and B) or over 8 weeks (Los Angeles C and D) symptom freedom is a good predictor for healing of the esophageal lesions [73-75]. However, there is no robust scientific rationale for requiring complete healing of reflux esophagitis and obtaining endoscopic remission (= healed reflux esophagitis). It is theoretically conceivable that patients with unhealed esophagitis will recur earlier. In placebo-controlled trials of long-term therapy for reflux esophagitis, patients with noncured esophagitis were excluded at the end of acute therapy, so this question cannot be answered on the basis of controlled trials. It is also conceivable that a continuing (chronic) inflammatory process per se increases the risk for carcinoma development. In a Danish population-based cohort study, the risk of carcinoma for patients with erosive esophagitis was greater than that for NERD patients and for the nonrefluxing general population [76]. However, the risk of carcinoma is very small in absolute terms. In the Danish cohort study, 37 of 26,194 patients with reflux esophagitis developed carcinoma within a median follow-up of 7.4 years, corresponding to an absolute 10-year risk

of 0.24% [76]. Thus, a carcinoma preventive effect will never be shown by a controlled study when viewed realistically.

Complications prevention

Maintenance of endoscopic remission would only be required if recurrence of reflux esophagitis was associated with an unfavorable prognosis for the patient. Symptom-adapted therapy cannot reliably prevent esophagitis recurrence as shown in a randomized trial comparing demand therapy with continuous PPI therapy in patients with reflux esophagitis of different severity levels [77]. The risk of recurrence increased with increasing severity of esophagitis in this study. Data on the natural (untreated) course of GERD are sparse in the literature and are not expected to be in the future given the availability of effective therapy. After the initial diagnosis of GERD in family practice, the risk of detecting esophageal adenocarcinoma and esophageal stricture is increased in the subsequent course [78]. However, in the vast majority of patients with reflux esophagitis, there is no progression of the disease in the long term, i.e., there is rarely an increase in severity, as shown by a systematic review of the available literature [79]. Of course, this does not exclude progression in individual cases. In the ProGERD study (progression of GERD under everyday conditions), only a few patients showed an increase in the initial severity of reflux esophagitis during a follow-up of 5 years under the care of a family physician [80]. In a Swedish population study with endoscopy and endoscopic follow-up, 12 of 90 patients with erosive esophagitis showed progression to higher severities and 8 showed development of Barrett's esophagus. The risk of progression was significantly lower in patients with NERD [81]. In a large unicenter cohort study, more than 2,000 patients with GERD received symptom-adapted treatment and were followed up for a mean of 7.6 years [82]. Among patients with reflux esophagitis, 11% had worsening esophageal findings during follow-up, and 1.9% developed stricture [82]. Acute bleeding from reflux esophagitis is observed predominantly in elderly and bedridden patients; otherwise, it is a rarity. Usually, they represent the initial diagnosis. Barrett's carcinoma is detected in more than 90% at initial endoscopy as shown in a Danish population study [83]. It remains unclear at present whether the risk of developing carcinoma on the floor of a Barrett's esophagus can be effectively reduced by drug or surgical therapy. There is evidence that early use of consistent and effective antireflux therapy may reduce the development of Barrett's esophagus and, consequently, Barrett's carcinoma [84].

Based on the available data, remission-maintaining therapy for esophagitis cannot be required for all patients; rather, it is important to identify and treat patients who are at high risk for complications during the course (e.g., severe esophagitis, complications that have occurred, elderly patients with absent or atypical symptoms).

Economic framework conditions

Economic conditions must also be taken into account when evaluating therapy goals. GERD is of considerable socio-medical relevance due to its high prevalence in the population and its often chronic course. The main cost factor in Germany is drug therapy, which accounts for 64% of total costs [85]. PPI are often prescribed without adequate indication, in too high doses and for too long [86]. Appropriate training has the potential to significantly reduce the frequency of prescriptions [87]. In management models derived from randomized controlled trials of acute and long-term therapy of patients with reflux

esophagitis, esomeprazole shows an advantage of >10% over omeprazole, lansoprazole, and pantoprazole with respect to the combined endpoint of healed esophagitis and clinical remission [88]. For this reason, an economic advantage is also possible through medication selection.

Recommendation 2.1 (new 2022)
A distinction should be made between therapy of reflux symptoms (without confirmed GERD) and that of confirmed GERD. (children and adults)
[Recommendation, strong consensus]

Comment:
The term "reflux complaints" implies that the underlying disease GERD is certain. However, typical reflux complaints (heartburn, regurgitation) are not suitable as a reliable diagnostic tool because they are neither sensitive (30% - 76%) nor specific (62% - 96%) [89]. The diagnostic quality cannot be relevantly improved by questionnaires or scores used in studies. Also the response of symptoms to PPI does not ensure the diagnosis of GERD [89].
To avoid erroneous therapeutic conclusions, it is important to differentiate between reflux symptoms without or with confirmed GERD, especially when symptoms do not respond adequately. This was shown in a large US study including 366 patients with PPI-refractory reflux symptoms [90]. A relevant proportion of these patients had a different cause of symptoms: 6% organic esophageal disease and 27% functional heartburn.

Recommendation 2.2 (new 2022)
Patients with reflux symptoms and those with confirmed GERD should be counseled about the importance of general measures in the therapeutic concept. (Children and adults)
[Strong recommendation, strong consensus]

Comment:
Obesity favors the development of GERD and its complications, presumably involving mechanical factors such as an increase in intra-abdominal pressure with a consecutive increase in the gastroesophageal pressure gradient and direct influences on the lower esophageal sphincter by mediators (e.g., adiponectin) [91-94]. Of course, this does not necessarily mean that weight loss obligatorily leads to an improvement in GERD. A systematic analysis of the available literature crystallized that weight loss may both improve symptoms and favorably affect pH-metric data in randomized controlled trials (*Table 6*) [95, 96]. The best available clinical evidence comes from the Scandinavian prospective and population-based HUNT study [97]. Weight loss was associated with improvement in reflux symptoms. There was also a correlation with the extent of BMI reduction. Similarly, weight reduction improved the efficacy of antireflux medication.
Raising the head of the bed can be recommended for patients with nocturnal reflux symptoms on the basis of 3 randomized controlled trials (*Table 6*). There is also supportive evidence for not eating late meals from 2 case-control studies and 1 randomized controlled trial (*Table 6*) [96, 98]. Left lateral position is a plausible explanation for reduced nocturnal reflux on anatomic grounds. In a pilot study of a

positional device designed to keep patients in the left lateral position for at least 6 hours, there was significant improvement in nocturnal reflux symptoms [99]. Four prospective controlled trials demonstrated an effect of breathing training (abdominal breathing) on reflux symptoms, pH and manometry findings, and PPI use (*Table 6*) [100]. In a population-based cohort study, smoking cessation led to symptom improvement in normotensive patients (*Table 6*) [97]. Tight clothing or tightly buckled belts should be avoided, as they lead to an increase in reflux, primarily by obstructing esophageal clearance [101].

Diet undoubtedly has an effect on reflux or reflux symptoms, although there is no specific antireflux diet (*Table 6*). An effect of selective interventions in dietary behavior such as reduction of alcohol consumption, avoidance of chocolate, coffee, spicy foods, citrus fruits, fatty foods, carbonated beverages has not been conclusively and universally demonstrated [95, 96, 98, 102]. The recommendation to avoid individually intolerable or unhealthy foods and beverages is nevertheless reasonable. Data from the Nurses Health Study showed that consumption of coffee, tea and carbonated mineral water was associated with an increased risk of reflux symptoms [103]. A reduction of fat and sugar intake in combination with an increased intake of dietary fiber seems advisable on the basis of pathophysiological considerations and experiments [104]. In a prospective study, a liberal diet was compared with a restrictive antireflux diet after appropriate training, and the effect was monitored pH-metrically. A highly significant and clinically relevant effect on esophageal acid exposure was demonstrated in the intraindividual comparison [105].

In a randomized study of 10 healthy controls and 10 patients with reflux esophagitis, sleep deprivation (≤3 hours of nighttime sleep) was shown to significantly increase the sensitivity of esophageal mucosa to acid [106].

Reflux symptoms are very common in athletes. An essential mechanism is - in healthy subjects - increasing reflux in the context of transient sphincter relaxations [107]. For this reason, GERD patients should be advised that sports with particular abdominal press are rather unfavorable.

Table 6: Effectiveness of general measures for GERD

Measure	**Effect on GERD parameters**	**Occupied by**	**Recommendation**
Weight loss	Improvement of symptoms and esophageal pH Reduction PPI consumption	RCT, case-control study	For patients who are overweight or have recently gained weight
Raising the head end of the bed	Improvement of symptoms and esophageal pH	RCT Case control study	For patients with nocturnal reflux symptoms
Diaphragm training (abdominal breathing)	Improvement of symptoms and esophageal pH Reduction PPI consumption	Case control study	With corresponding treatment request

Avoidance of late meals	Improved nocturnal acidity	Case control study	For patients with nocturnal reflux symptoms
Stop smoking	No effect on symptoms and esophageal pH	Case control study	Generally good recommendation, effective for normal weight smokers
Diet	Improvement of symptoms and esophageal pH	Case control study	Individualized nutrition counseling

Recommendation 2.3 (modified 2022)

A standard-dose PPI** should be prescribed for typical reflux symptoms with no alarm symptoms, no positive family history of upper gastrointestinal tract malignancy, and no risk factors for complications*. (Children and adults)

*Severe reflux esophagitis (Los Angeles grade C and D, peptic stenosis, Barrett's esophagus).

**according to the approval status of the individual preparations

[Recommendation, strong consensus]

Comment:

Patients with typical reflux symptoms requiring treatment (heartburn, acid regurgitation, regurgitation) without alarm signs or risk factors (e.g., weight loss, dysphagia, evidence of bleeding, family history of upper gastrointestinal tract malignancies, long-standing severe reflux symptoms, especially including nocturnal symptoms) can be treated empirically with a standard-dose PPI without endoscopy [98, 108]. Since there is no discriminating correlation between frequency and severity of symptoms on the one hand and endoscopic findings on the other hand [109, 110]In such a situation, the presence or severity of lesions or even pre-existing complications (e.g., Barrett's esophagus) in the esophagus cannot be reliably inferred. Full-dose PPI therapy for 4 weeks is an adequate therapy for symptom control and healing of any lesions for patients with NERD as well as for the vast majority of patients with erosive esophagitis. In addition, the most effective therapy with a rapid onset of action is in line with patient preference. In a randomized trial, 612 patients with GERD symptoms were treated either empirically with 40 mg esomeprazole for 4 weeks or endoscopically with subsequent 40 mg esomeprazole for esophagitis patients and 20 mg esomeprazole for NERD patients. After 4 weeks, treatment success was comparable: 86.4% vs. 87.5%, respectively [17]. In a multicenter, open-label study, 2,156 patients with heartburn were treated with 40 mg esomeprazole on at least 3 of 7 days in the previous week. After 4 weeks, 88% of patients were symptom-free [111]. In a large, randomized, double-blind study, 593 outpatients with heartburn were treated for 20 weeks. Compared 30 mg lansoprazole, 2x150 mg ranitidine with a step-down regimen consisting of 30 mg lansoprazole for 8 weeks followed by 2x150 mg ranitidine and a step-up regimen consisting of 2x150 mg ranitidine for 8 weeks followed by 30 mg lansoprazole. The continuous lansoprazole treatment was superior to the other three treatment

regimens in terms of severity of heartburn and number of days without heartburn [112]. A Cochrane review identified 15 randomized trials of empiric therapy for reflux symptoms. In placebo-controlled trials and in head-to-head comparisons, PPIs were more effective than H_2 -receptor antagonists and prokinetics [113].

A number of issues related to symptom-based treatment have not been sufficiently clarified. This concerns, for example, the necessary duration of acute therapy. In a purely symptom-based treatment, one would end the therapy with the onset of symptom freedom. The recommendation of a four-week therapy corresponds to the study situation. In addition, this results in effective treatment of any esophagitis that may be present.

Recommendation 2.4 (modified 2022)

In typical reflux symptoms without alarm symptoms, without a positive family history for malignancies of the upper digestive tract and without risk factors for complications, other antireflux preparations (e.g. H_2 receptor antagonists, alginates, antacids) can also be used on a trial basis if symptom control is sufficient from the patient's perspective. (Children and adults)

[Recommendation open, strong consensus]

Comment:

In a randomized, double-blind, double-dummy study in patients with heartburn without alarm symptoms on 2-6 days in the preceding week, 14 days of therapy with an alginate (4x per day) was noninferior to therapy with 20 mg omeprazole [114]. It must be mentioned restrictively that the effect of alginates on reflux esophagitis is unknown. Risk factors for severe esophagitis, peptic strictures, and Barrett's metaplasia are male gender, older age, longstanding, especially nocturnal reflux symptoms, smoking, and central obesity. H_2 -receptor antagonists have long been established for the treatment of reflux symptoms, less effective than PPI, but more effective than placebo [115]. Antacids are commonly used in self-medication. They also serve as on-demand medication in placebo-controlled trials. In a meta-analysis of randomized controlled trials, they were inferior to alginates [116].

Recommendation 2.5 (modified 2022)

In case of inadequate or absent response of typical reflux symptoms without previous diagnosis to PPI therapy adequately performed for at least 8 weeks, further clarification should be performed (children and adults).

[Recommendation, strong consensus]

Comment:

There is no universally agreed upon definition for "PPI-refractory reflux symptoms" [117]. Adequately performed in this context means that it is a correct intake of a PPI in a dosage approved for this indication. The literature also includes recommendations such as PPI therapy at twice the standard dose for up to 12 weeks [115]. This is an off-label approach that is not supported by scientific data. This statement does not take into account that the PPIs on the market differ significantly in their effect on

intragastric acidity [118, 119]. In studies in NERD patients, who make up the majority of reflux patients, the extent of acid inhibition did not play a role in symptom control [120]. Even in patients with reflux esophagitis, the difference between individual PPIs in terms of symptom control is marginal. Studies in NERD patients were conducted over 4 weeks, while those in reflux esophagitis were conducted over 4-8 weeks.

Recommendation 2.6 (modified 2022)

In cases of confirmed or probable GERD, PPI therapy should be given for at least 4 to 8 weeks. PPI dosage should be based on the phenotype of GERD and the approval status of the selected PPI. (Children and adults)

[Strong recommendation, strong consensus]

Comment:

Definitive confirmation of the diagnosis of GERD according to the Lyon Consensus is often not possible in practice, since - with few exceptions - it would require functional diagnostics with pH-metry or, better, impedance-pH-metry [120]. However, the approval of PPIs is based on appropriate studies including patients with NERD, defined as typical reflux symptoms without endoscopic evidence of reflux esophagitis, and patients with reflux esophagitis with varying severity (mucosal breaks) of the esophagus according to the Los Angeles classification.

Patients with NERD represent a pathophysiologically heterogeneous group: Only about half of the patients show a pathological acid reflux that can be detected by pH-metry; in the other patients, pH-metry is normal. In the latter group of patients, about one third have a hypersensitive esophagus (to acidic [pH<4] or non-acidic reflux), i.e., they perceive physiological reflux episodes, and two thirds suffer from so-called functional heartburn, i.e., the complaints are independent of reflux events [121]. This explains that patients with NERD respond worse to PPI therapy in terms of symptoms than patients with reflux esophagitis. In a systematic review, the therapeutic gain over placebo after 4 weeks of therapy with a PPI was 27.2% in NERD patients and 48.0% in esophagitis patients ($p<0.0001$) [122]. If one narrows the definition of NERD, i.e. considers only patients with negative endoscopy and positive test result of pH-metry, then on the basis of a meta-analysis the symptomatic effect in patients with NERD and esophagitis are comparable [123].

In acute drug therapy of NERD, PPIs are superior to other therapeutic principles (H_2 -receptor antagonists, prokinetics) with regard to the primary therapeutic goal of symptom relief [113]. To some extent, the extent of acid inhibition plays a role in symptom relief. For example, omeprazole 20 mg is more effective than 10 mg and also than 150 mg ranitidine [121]. Increasing beyond 20 mg omeprazole equivalent, on the other hand, does not generally appear to be useful, as shown by three large, randomized, double-blind trials of 20 mg omeprazole, 20 mg esomeprazole, and 40 mg esomeprazole [120]. Patients with hypersensitive esophagus who benefited from high-dose omeprazole therapy in a randomized controlled trial may be excluded from this finding [124]. Alginates may represent a comparably effective alternative to PPIs [114], however, a formal study in patients with NERD is not available.

The initial therapy is recommended for mostly 2-4 weeks [121]. However, it is unclear whether patients who are symptom-free after 3 days, for example, actually benefit from longer therapy. Since it is

theoretically conceivable that the pathophysiological mechanisms at the mucosal level involved in symptom generation (e.g., inflammation, increase in neural plexuses and receptors, dilation of intercellular clefts) may take longer to achieve restitution than symptom relief itself, a recommendation that deviates from the study situation does not seem appropriate [125]. Experimentally, it can also be shown that repetitive acid infusions in the esophagus lead to persistent hypersensitivity [126].

Data on the effectiveness of antacids in patients with NERD are lacking. They have been and are often used for additional symptomatic treatment in both the verum and placebo arms of controlled trials. The placebo effect should also not be underestimated: In a meta-analysis, it was 18, % in NERD patients [127]. However, antacids are not without side effects, especially when taken in larger doses. There are no objections to occasional use for sporadic complaints [69, 98].

Endoscopically visible reflux esophagitis - in contrast to NERD - is frequently associated with pathologic acid reflux. Accordingly, inhibitors of acid production (PPI, H_2 -RA) have been effective in numerous placebo-controlled studies in terms of symptom relief and cure of esophagitis [128]. PPIs are more effective than H_2 -RA in direct comparison and are therefore the therapy of choice [98, 128]. Symptom relief with PPIs occurs after a median treatment duration of 5-10 days with no established dependence on the severity of esophagitis [73-75]but on the extent of acid inhibition [129]. In a randomized controlled trial, obese patients with mild reflux esophagitis (Los Angeles A and B) were shown to benefit in terms of symptomatic response from a double dose of pantoprazole (2x40 mg) compared to the standard dose of 40 mg [130]. However, persistent reflux symptoms are more common than persistent esophagitis [73-75, 131]. The speed of recovery from esophagitis depends on the extent of acid inhibition, the duration of therapy in weeks, and the severity of the reflux esophagitis [73-75, 131-133]. The duration of time with pH values above 4 per 24 hours is considered a pharmacologic surrogate marker.

In the vast majority of studies, the approved standard doses of the different PPIs were investigated and an endoscopic healing control was performed after 4 weeks and again after 8 weeks if healing did not occur. In mild esophagitis (Los Angeles A and B), high cure rates were observed after only 4 weeks, whereas patients with severe esophagitis (Los Angeles C and D) require an eight-week therapy to a relevant extent. Since cure monitoring is not a standard part of clinical routine, a pragmatic approach recommended is a therapy duration derived from the study data based on the severity of reflux esophagitis. In a randomized trial, the recurrence rate of mild reflux esophagitis (Los Angeles grade A/B) after 12 weeks was significantly lower when initial therapy was given for 8 instead of 4 weeks [134]. For this reason, the recommendation of an 8-week initial therapy for all patients with reflux esophagitis also seems reasonable.

The question of whether there are clinically relevant differences between individual PPIs is controversial. The individual PPIs differ significantly in cross-over studies with regard to the effect on intragastric acidity, and the predictability of the pH-raising effect also varies 54 . In a meta-analysis of randomized trials (n=10), small advantages were found for esomeprazole over other PPIs in terms of symptom relief at 4 weeks (8% relative increase) and esophagitis cure at 8 weeks (5% relative increase) [135]. However, particularly in severe esophagitis (Los Angeles grade C/D), significant and clinically relevant benefits of 40 mg esomeprazole over other PPIs at their standard doses are seen at 4 and 8 weeks [133].

In placebo-controlled trials, H_2 -RA were more effective than placebo and antacids, but the effect is significantly worse than that of PPIs. In a systematic review that included 9 randomized controlled trials,

esophagitis persisted in 42% of patients after 12 weeks of therapy with an H -RA_2 compared with 63% on placebo [136]. Antacids and prokinetics have no established effect on esophagitis [136]. No data are available for alginates with regard to healing of esophagitis.

Recommendation 2.7 (new 2022)

In cases of confirmed or probable GERD and inadequate response to a standard dose of a PPI, switching to another PPI, doubling the dose of the PPI (1-0-1), or combination therapy with another active principle* may be used. (Children and adults)

*e.g. alginate

[Recommendation open, strong consensus]

Comment

Inadequate symptom control under PPI is a common phenomenon in GERD patients in treatment and population studies [117, 118, 137].

If symptom control is inadequate after 4 weeks, the duration of therapy may be extended [138]. Other options include increasing the PPI dose to 2x1 standard dose or (especially if pantoprazole is used) switching to a different PPI [139, 140]. This takes into account the individual differences in response to different PPIs [141]. Another option is to combine the PPI with an alginate 4 times a day or as an add-on if required [142-144] although the studies on this are not uniform [145]. Other preparations that can be considered as combination partners for PPI are antidepressants, as these substances can increase the threshold of irritation in the esophagus [129]. However, an indication exists only for hypersensitive esophagus, i.e., an appropriate functional diagnosis must have been performed. Baclofen (possibly also gabapentin) acts on the lower esophageal sphincter and can thereby reduce the number of reflux episodes [90, 146]. The problem with this substance is its unfavorable side effect profile. One should therefore limit its use to justified individual cases only. Ex juvantibus and based on pathophysiological considerations, prokinetics (especially in cases of concomitant dyspeptic problems) and H_2 blockers are occasionally used at night (treatment of nocturnal acid reflux), although no randomized clinical studies have been conducted to date that document a therapeutic benefit [147].

Recommendation 2.8 (new 2022)

In refractory GERD, defined as inadequate response to at least 8 weeks of therapy with twice the dose of a PPI (1-0-1), further evaluation should be performed. (Children and adults)

[Strong recommendation, strong consensus]

Comment:

In such a clinical situation with confirmed GERD and correctly administered PPI therapy, the issue is to prove or exclude clinical scenarios that account for the inadequate PPI effect. PPIs can be satisfactorily effective only where acid (in the wrong place) is the major pathogenetic factor [137, 148]. PPIs are particularly effective in healing reflux esophagitis, but they are significantly less effective in achieving satisfactory symptom control.

If symptoms persist despite adequate, high-dose PPI therapy in patients with confirmed GERD, the first step is to determine whether they are typical reflux symptoms that persist. Patients with GERD may have concomitant diseases such as coronary artery disease (CAD), irritable stomach, or irritable bowel syndrome. It is not uncommon for patients to have a somatization disorder, which can be suspected or recognized by a variety of symptoms that often cannot be attributed to a single cause [149]. For this reason, all symptoms should be recorded and it should be explicitly asked which symptom(s) do not respond to PPI. If the symptoms are typical reflux symptoms, there are basically 5 main mechanisms that explain symptom persistence [117]:

1. PPI did not normalize esophageal acid exposure

PPIs vary in their effect on intragastric acidity. Relative to 20 mg omeprazole (defined as 1.0), the relative efficacy of standard doses of pantoprazole 0.23, lansoprazole 0.90, esomeprazole 1.62, and rabeprazole 1.82 is [119, 150]. In addition, patients respond differently to PPIs (87). With the exception of 2x40 mg esomeprazole, sufficient acid control cannot be reliably predicted with any PPI [119]. In addition, GERD patients (without *HP infection*) require higher doses of a PPI for adequate acid control than healthy subjects and *HP-infected* patients [119].

2. PPI have normalized acid exposure time, but reflux events persist causing heartburn (reflux hypersensitivity)

Before the introduction of impedance pH-metry, the term "hypersensitive esophagus" was used when GERD symptoms were experienced in the setting of physiologic acid reflux. Impedance pH metry has been used to demonstrate that nonacid reflux events (pH≥4) can also produce symptoms. For this reason, we should speak of "reflux hypersensitivity" [117]. Significant correlation is captured by the symptom index (SI) or the probability of symptom association (SAP) , which is presumably less susceptible to interference for mathematical reasons.

3. Heartburn is caused by esophageal disease other than GERD

Any other inflammatory esophageal disease can cause retrosternal burning. The most common misdiagnosis probably occurs in eosinophilic esophagitis, when retrosternal burning is the dominant symptom [117]. This disease is excluded or detected endoscopically and biopsy. However, it should be kept in mind that both endoscopic and histologic signs may disappear with PPI therapy, so that a finding that is unremarkable in this regard does not rule out this disease. Accordingly, if possible, the already ineffective PPI therapy should be paused for 3-4 weeks before the planned endoscopy. Patients with achalasia also frequently complain of heartburn, which can lead to a misdiagnosis of GERD and a misindicated fundoplication [151]. For this reason, high-resolution manometry should be performed, especially before any antireflux surgery.

4. Heartburn due to extraesophageal disease

Diseases of organs of the thorax and upper abdomen can cause retrosternal symptoms, which in individual cases are confused with heartburn [117]. Of particular clinical relevance here is CHD, especially since patients with CHD and GERD have an overlapping risk profile (e.g., obesity) [152]. On the other

hand, the symptom angina pectoris in the sense of non-cardiac chest pain is also part of the typical spectrum of GERD[153].

5. Functional heartburn

According to the current version of the ROME IV criteria, "functional heartburn" is defined as retrosternal burning, pain, or discomfort despite optimal antisecretory therapy and after exclusion of GERD, histologic mucosal changes, defined motility disorders, and other structural explanations [154]. The diagnosis can only be confirmed by appropriate exclusion diagnostics, in patients with confirmed GERD this requires elimination of pathological acid reflux by PPI therapy and evidence of reflux-independent symptoms on impedance pH-metry.

From these basic considerations, an algorithm can be developed for rationally and rationally moving from PPI-refractory "heartburn" to a clear cause assignment and treatment strategy (*Figure 2*) [115]. In principle, this algorithm has been validated by a multicenter study in the U.S. [90]. It should be explicitly mentioned that the algorithm is not primarily designed to confirm or exclude the diagnosis of GERD, but to manage a common therapeutic problem - PPI-refractory heartburn - whose most common but not sole cause is GERD.

Limiting the diagnosis or exclusion to GERD would not solve the problem in this clinical situation, as other causes may be solely responsible or coexistent.

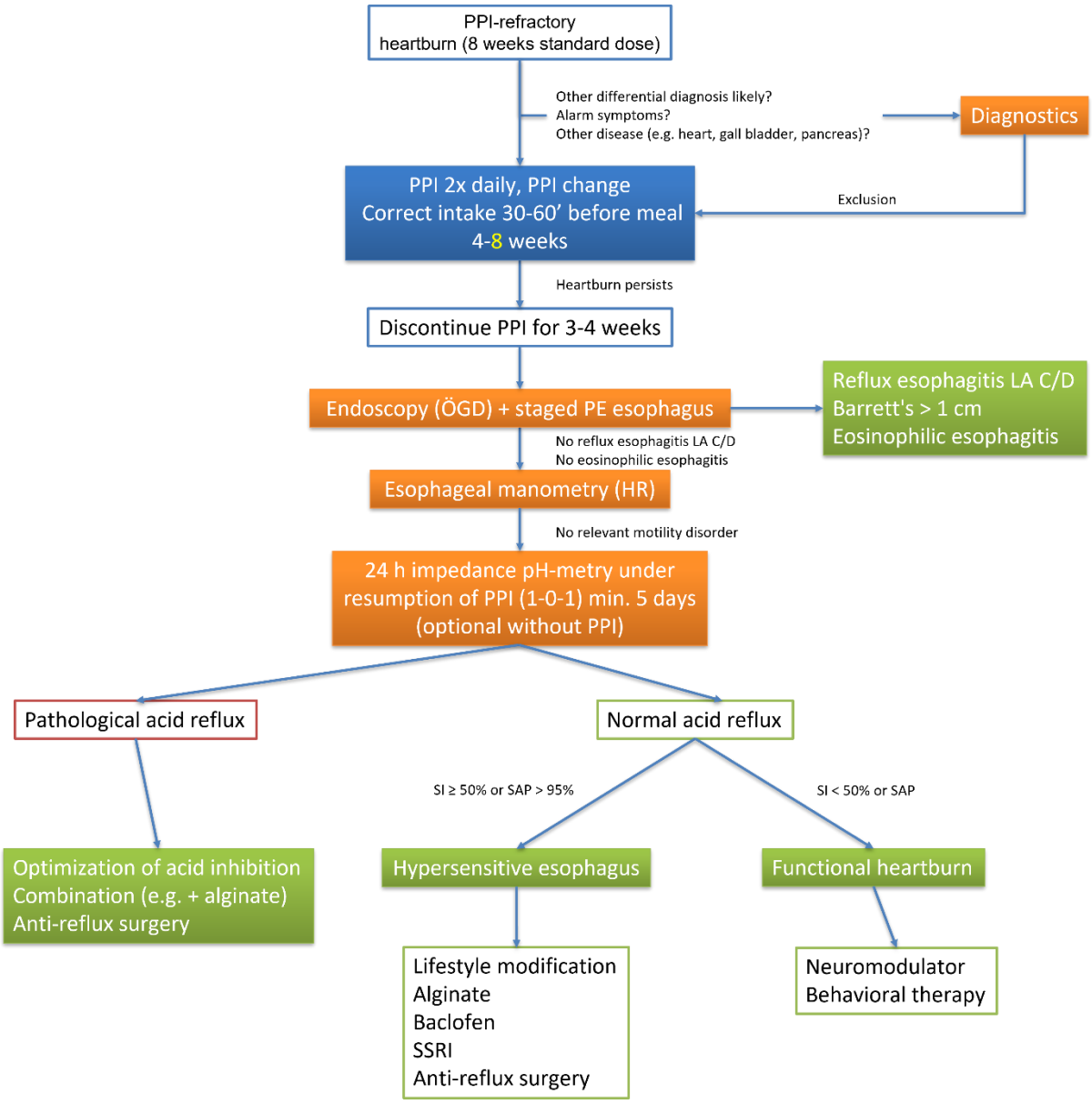


Figure 2: Algorithm for the management of PPI-refractory heartburn for adults and older children (after [115]) (consensus)

6. Regurgitation-dominant GERD

In studies, the therapeutic success is often evaluated or reported only with regard to the leading symptom "heartburn". The therapeutic gain of PPI over placebo was more than 20% lower for regurgitation than for heartburn, at only 17%, in 7 controlled trials [155-158]. H_2 -RA and prokinetics showed a placebo-level effect in comparative studies with PPI [156]. In a large randomized controlled trial of 1,460 NERD patients treated with a PPI or a P-CAP (potassium competitive acid blocker) for 4 weeks, 53% of patients complained of severe regurgitation. Symptomatology responded significantly worse to acid blockade than to heartburn [157]. In an observational study involving 134 centers in 6 European countries, 12-13% of reflux patients with well-controlled heartburn continued to suffer from frequent regurgitation [158].

Acidity plays only a minor role in regurgitation, whereas the volume of the refluate is of greater relevance. PPIs mainly influence the acidity of the reflux, the effect on the volume is small. Pathophysiologically,

incompetence of the antireflux barrier is the primary concern. Dysfunction of the upper esophageal sphincter also occurs [155]. Differential diagnosis should be based on achalasia, rumination and gastroparesis [137].

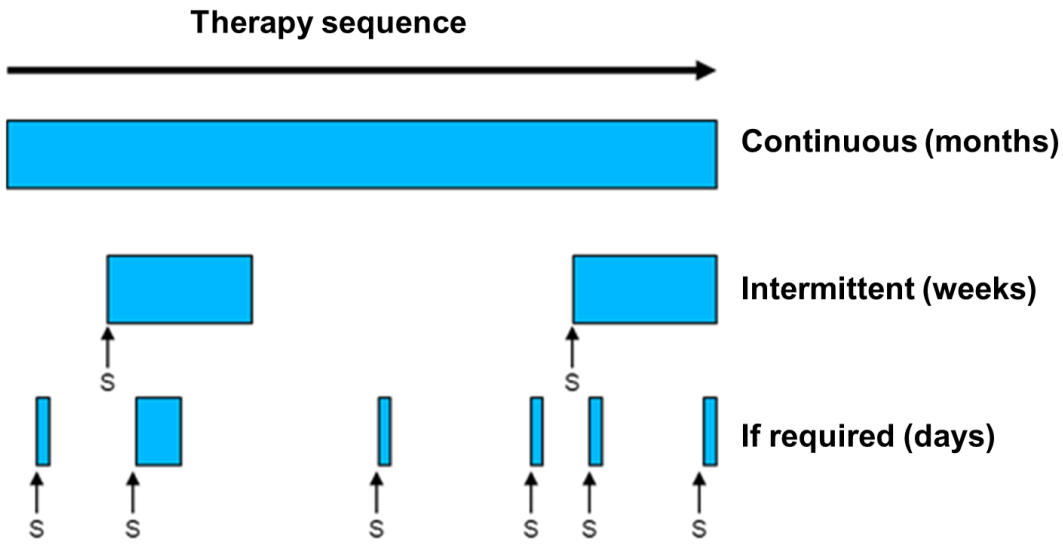
Recommendation 2.9 (new 2022)

In uncomplicated GERD (NERD, mild Los Angeles reflux esophagitis grade A/B), long-term medical management should be based on symptoms. Overtreatment should be avoided. (Children and adults) [Recommendation, strong consensus] *(Decide Wisely).*

Comment:

Patients with NERD and mild reflux esophagitis (Los Angeles grade A/B) are at low risk of developing serious complications over time. Because mild reflux esophagitis is progressive over time in only a few cases, a symptom-adapted strategy suffices [80, 82]. For this reason, the long-term satisfactory control of symptoms with normalization of the quality of life and preservation of the ability to work is in the foreground. Theoretically, all patients who respond to PPI could be treated with continuous PPI therapy. However, this would mean overtreatment for many patients, as a significant proportion of patients with NERD and mild reflux esophagitis do not relapse or relapse rarely, or at least remain symptom-free for a longer period of time [159, 160]. Intermittent courses of therapy or a purely as-needed strategy, in which the patient takes a medication in case of symptoms or situations that typically trigger symptoms and also stops the therapy immediately if symptoms persist, come as an economical alternative to continuous long-term therapy (*Figure 3*). Demand therapy has been investigated in a number of carefully controlled studies and has been established in routine clinical practice [121, 161-163]. In each case, patients who had been symptom-free for 4-8 weeks on acute therapy were treated. The primary objective was treatment satisfaction combined with the desire to continue this therapy, i.e., treatment discontinuation was defined as a surrogate for patient dissatisfaction and inadequate symptom control. In five placebo-controlled trials, this was achieved in 83%-94% of patients with 20 mg omeprazole or half the standard dose of another PPI. In this respect, demand therapy was superior not only to placebo but also to continuous (daily) PPI use and is therefore now considered the treatment of choice (*Figure 4*).

In principle, therapy with other drugs is also possible or permitted, provided the patient has NERD and symptom control is judged to be satisfactory. In the placebo arms of the above-mentioned studies, 48% to 72% of the patients were satisfied with the therapy (antacids allowed). This suggests that other medications - in this case antacids as needed - also lead to satisfactory symptom control in a relevant proportion of patients.



S = Symptom relapse

Figure 3: Strategies for long-term therapy of reflux disease (children and adults) (consensus)

In a randomized, controlled trial that included 477 patients with reflux esophagitis of all severities (Los Angeles grades A-D) and compared esomeprazole 20 mg daily or as needed, no difference was found with respect to symptom control but was found with respect to the incidence of esophagitis recurrence, which was lower with continuous administration than with as-needed therapy for all severities of esophagitis [77]. The frequency of esophagitis recurrence increased with esophagitis severity. Because patients with mild reflux esophagitis rarely develop progression to severe esophagitis and mild esophagitis is also not uncommon (6% in a Scandinavian population study) in the healthy general population, this higher recurrence rate can be accepted without relevant risk to patients (*Figure* 4) [80, 164].

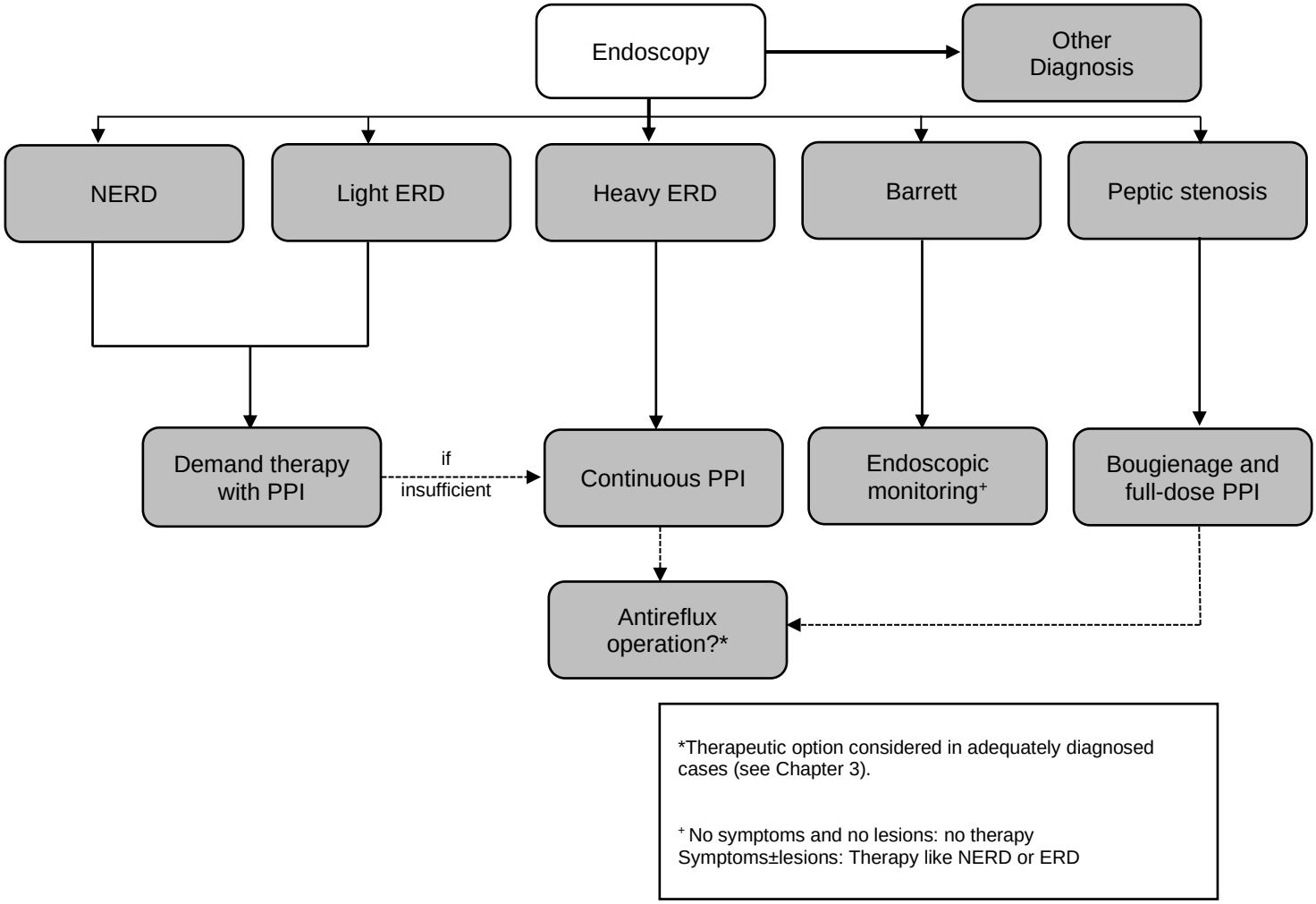


Figure 4: Algorithm for long-term management of GERD depending on endoscopic findings (children and adults) (consensus)

Recommendation 2.10 (new 2022)
In complicated GERD (reflux esophagitis grade C/D, peptic stricture), PPI continuous therapy should be given. (Children and adults)

[Recommendation, strong consensus]

Comment:
Severe reflux esophagitis may be the starting point of complications such as hemorrhage and stenosis. Furthermore, in controlled studies, approximately 90% recurrences were observed within the first weeks after discontinuation of an initially successful curative therapy with a PPI [165-167]. Based on this experience, the principle of recommending long-term therapy immediately after acute therapy (*Figure 4*). On the basis of a randomized controlled trial, symptom-controlled PPI therapy is not sufficient to maintain remission of esophagitis [77]. Also in the long-term course, the extent of acid secretion inhibition and the severity of reflux esophagitis according to the Los Angeles classification are predictors of therapeutic success [168-172]. In a review, data from 4 comparative clinical trials were correlated with data

from pharmacologic studies examining intragastric acidity under different PPIs. An inverse, nonlinear correlation was found between time with gastric pH values above 4 and remission maintenance of esophagitis [173].

Peptic stricture has become much less common since the introduction of PPIs. Effective acid inhibitory therapy is critical for long-term success or maintenance of remission after dilatation [174].

Recommendation 2.11 (modified 2022)

If an extraesophageal manifestation of GERD is suspected in adults, PPI therapy should be given at twice the standard dose (1-0-1) for 12 weeks. Children and adolescents should be diagnosed first.

[Strong recommendation, consensus]

Comment:

Few areas are as controversial as the existence and management of so-called extraesophageal manifestations of GERD. According to the MONTREAL consensus, cough, asthma, laryngitis (synonymously laryngo-pharyngeal reflux (LPR) ; symptoms: Globus, compulsive throat clearing, voice problems) and dental erosions are considered "established" associations [2]. Association, however, does not equate to causality. In the presence of these problems, which are extremely frequent in general and specialist practice, a reflux genesis should be considered in individual cases - after exclusion of other causes - and especially in the case of coexistence of typical reflux symptoms, although a causal relationship is probably much rarer than previously assumed [175]. Microaspiration or vago-vagal reflexes triggered by reflux as a primarily plausible pathophysiological concept are not sufficient to explain the overall disappointing results of intervention studies [118]. It is likely that even in patients with confirmed GERD, reflux is only one (possible) of several triggers that may trigger symptoms via stimulation of receptors. This then also explains the persistence of symptoms despite adequate PPI therapy.

Efficacy compared with placebo has been demonstrated in randomized trials for cough in objectified GERD (33% vs. 9%) [137, 175, 176]. In asthma, a subgroup with nocturnal respiratory and typical reflux symptoms may also benefit [175, 177, 178]. For laryngitis, there is a placebo-controlled study (82 patients) with 2x20 mg rabeprazole for 12 weeks that showed a positive effect on symptoms [179]. The largest study, which included 145 patients and treated with 2x40 mg esomeprazole or placebo for 16 weeks, showed no effect [180]. A recent meta-analysis concluded that PPIs probably have a small effect, but due to the heterogeneity of the studies, no firm conclusions can be drawn [181]. No data from placebo-controlled studies are available for PPI therapy in patients with dental erosions.

When an "established extraesophageal manifestation" (cough, asthma, laryngitis, dental erosions) of a known, suspected, or considered GERD is suspected, in the absence of diagnostic measures conclusively demonstrating a causal relationship between the complained symptoms and GERD, high-dose PPI therapy for up to 12 weeks is recommended as a first step in adults. This recommendation is justified by studies that have shown an effect over placebo. It is also recommended to select a PPI with a high likelihood of achieving adequate gastric acid control (e.g., 2x40 mg esomeprazole) (*Figure* 5). This recommendation cannot be applied to children, as relevant studies are lacking. Therefore, reflux diagnostics should always be performed as a first step in children. In case of satisfactory control of

extraesophageal symptoms, individual titration to the lowest, still effective PPI dose is recommended. If there is no improvement in extraesophageal symptoms, PPI therapy should usually be discontinued in the absence of typical reflux symptoms. If doubts remain as to whether GERD is present, impedance pH-metry without medication is recommended. If typical reflux symptoms are also present with a reasonable suspicion of GERD, further diagnostics including an esophago-gastro-duodenoscopy (ÖGD) and impedance pH-metry are recommended. OGD should look for heterotopic corpus-type gastric mucosa (inlet patches) in the proximal esophagus, as these can sometimes cause laryngopharyngeal symptoms and are amenable to endoscopic ablation [182]. Impedance pH-metry without PPI is used to detect GERD, with examination under ongoing high-dose PPI therapy there is an option to detect persistent acidic (pH<4) and nonacidic reflux (pH≥4) including extension into the esophagus (proximal reflux) and association to complained symptoms.

For H_2 receptor antagonists, prokinetics, baclofen, and gabapentin, there are no data to justify their use as monotherapy; for add-on treatment with a PPI, the data are inconclusive [175]. Alginates have been studied in 2 randomized trials in LPR. In an open-label trial, a significant effect on symptom scores was found compared with no treatment [181]. In contrast, a randomized, double-blind, placebo-controlled trial failed to demonstrate efficacy over placebo [183]. In the latter study, a pronounced placebo effect was evident.

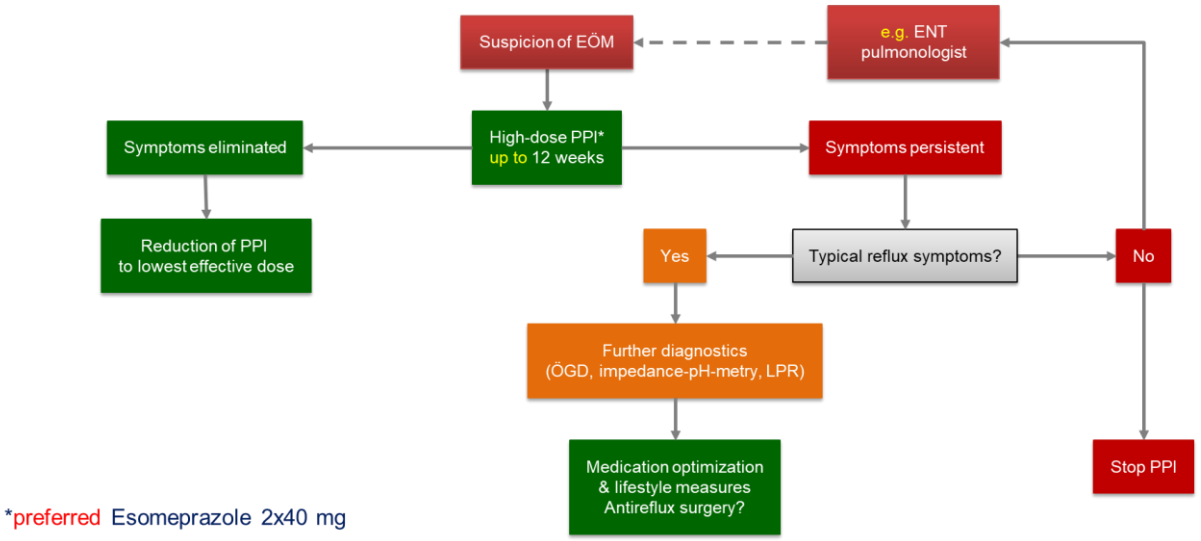


Figure 5: Algorithm for management of suspected extraesophageal manifestation of GERD in adults

Recommendation 2.12 (modified 2022)

If reflux thoracic pain syndrome is clinically suspected, therapy with twice the standard dose of a PPI (1-0-1) should be given for 8 weeks. (Children and adults)

[Recommendation, strong consensus]

Comment:

Chest pain that is clinically indistinguishable from ischemic heart pain may be a symptom of GERD (= reflux chest pain syndrome) without typical reflux symptoms such as heartburn or regurgitation being present [2]. GERD is the most common cause of noncardiac thoracic pain [178]. Probatory therapy with a

PPI for suspected reflux thoracic pain syndrome is diagnostic with acceptable goodness criteria as shown by two independent meta-analyses [184, 185]. This should be carried out for at least 2 weeks [186]. In a systematic review on the therapy of noncardiac chest pain, Hershcovici et al. found, in addition to 4 uncontrolled studies, 8 randomized controlled trials with PPI therapy [187]. The studies were predominantly small. Based on this limited data, the authors concluded that therapy with a double dose of a PPI (1-0-1) should be given for at least 8 weeks. The recommendation for 8 weeks of therapy was based largely on the results of a large study of 599 patients in family practice who were treated with 2x40 mg esomeprazole for 4 weeks. In this study, a known reflux disease or one that could be suspected from the symptoms was an exclusion criterion [188]. Under these conditions, PPI therapy was more effective than placebo, but the difference was small with 33.1% vs. 24.9% pain relief (p=0.035). In a systematic review, Kahrilas et al. found 6 randomized controlled trials in which GERD was confirmed or excluded by endoscopy and/or pH-metry [189]. The duration of therapy was 1, 2, 4, or 8 weeks. PPIs were significantly more effective than placebo in confirmed GERD, whereas the response in patients without GERD was at the placebo level. Another significant finding was that symptoms improved but, for the most part, were not completely eliminated.

Of particular clinical relevance, patients with confirmed coronary artery disease may also benefit from PPI therapy with respect to their chest pain [190]. It follows that in cases of unexplained chest pain, a response to trial PPI therapy does not exclude coronary artery disease. In a cohort study, the risk of developing CHD was slightly increased with PPI therapy because of noncardiac chest pain, but the odds ratio was 1.14 (95% confidence interval 1.03-1.25), in a range that does not allow reliable inference of causality [191].

In a review, George et al. concluded that based on the current evidence, PPI therapy for 2 months is a reasonable first step; alternatively, a diagnostic therapy trial with a PPI for 1-2 weeks can be performed [192]. If the therapy is successful, a reduction of the PPI to the lowest effective dose is recommended. If adequate symptom control does not occur under high-dose PPI therapy, impedance pH-metry under continued PPI therapy is recommended to differentiate between inadequate PPI therapy (persistent acid reflux), reflux hypersensitivity and symptomatology not due to reflux.

Recommendation 2.13 (modified 2022)

Patients with sleep disturbances in the setting of GERD may be treated with a PPI and/or an alginate at night. (Children and adults)

[Recommendation open, strong consensus]

Comment

Epidemiologic case-control studies show a disproportionate association between sleep disorders and GERD. Reflux can lead to sleep disturbances, but sleep disturbances in turn can provoke or aggravate gastrointestinal disorders including reflux [193]. Previously, it was assumed that reflux occurs during a stable sleep phase and that this then leads to awakening. In a systematic review, Dent et al. analyzed all studies that addressed the pathomechanisms of sleep disturbances in the setting of GERD [194]. According to these, it seems more likely that reflux occurs during periods of CNS activation with or

without awakening and then leads to sleep disturbances via delayed clearance of reflux. In a recent study, the reflux followed the waking phases [195].

A systematic review identified 8 randomized, placebo-controlled trials of the efficacy of PPI therapy for reflux-associated sleep disorders [196]. Seven of the 8 studies, with patient numbers ranging from 15 to 642, showed significant superiority of PPI over placebo. The smallest study showed no effect [197]. It was conducted with 2x40 mg esomeprazole and had as a special feature a "provocation meal" 1 hour before bedtime. In two studies, polysomnography was performed without evidence of statistically significant improvement with PPI. In 4 of the 8 studies, PPI was taken in standard doses in the morning, in 3 studies in double doses in the morning and evening, and in one study, the time of intake was not specified for once-daily dosing. The 3 largest studies by far used the PPI in the morning (before breakfast). The studies were so heterogeneous in terms of their design that a meta-analysis to estimate the treatment effect did not seem useful. The duration of therapy varied between 2 and 8 weeks. In a large randomized trial in primary care practices, 825 of 1,388 patients with GERD had sleep disturbances. They were randomized either to continue treatment unchanged for 4 weeks or to switch to 20 mg or 40 mg esomeprazole. Sleep disturbances persisted in 55% of patients with unchanged management and in 22.5% of patients on PPI corresponding to an NNT of 3 [198]. The decrease in sleep disturbances was associated with a significant improvement in quality of life.

Controlled data on long-term therapy of sleep disorders are not available. In the ProGERD study, 4,597 of initially 6,215 reflux patients were followed up for 5 years in primary care with annual review of quality of life using the QOLRAD, which includes the sleep disturbance dimension. Compared with baseline, 61% of patients reported improvement in their sleep disturbances, 35% reported no change, and 4% reported worsening [199].

In a randomized, double-blind, placebo-controlled study of 16 GERD patients and 8 controls, zolpidem was shown to significantly reduce the effect of esophageal acid exposure on activations of the CNS . In addition, a significant prolongation of esophageal acid exposure time was observed in both reflux patients and controls [200].

Not synonymous with sleep disorders in the context of GERD is sleep-associated GERD as a clinical entity. Many GERD patients (also) have nocturnal reflux symptoms or nocturnal reflux. Patients with nocturnal GERD are more likely to have more complicated disease with a tendency to esophagitis and respiratory complications than patients who have only daytime GERD [201].

The acid pocket is a reservoir for acid reflux. In a randomized study, it was shown that an alginate, but not an antacid, succeeded in eliminating the acid pocket after a late-night meal. [202]. No study exists that examined the effect of alginate on sleep disturbances as a primary study objective. In a placebo-controlled study, alginates significantly increased the number of symptom-free nights in GERD patients with inadequate PPI effect [143]. Improvement in sleep disturbances was also described in an uncontrolled study with alginate as an add-on when needed for inadequate PPI effect [144].

Recommendation 2.14 (new 2022)

Step-up management should be used for reflux symptoms in pregnancy: General measures, antacid, alginate, sucralfate, H_2 -receptor antagonist, PPI.

[Recommendation, strong consensus]

Comment:

Gastrointestinal complications are common in pregnancy. This is especially true of GERD, which affects between 40% and 85% of pregnant women [203]. The condition can occur at any time during pregnancy and ranges from occasional, tolerable reflux symptoms to serious lesions of the esophagus, although these rarely occur [204]. In a prospective longitudinal study in Germany of 510 pregnant women, 26.1% of women complained of reflux symptoms in the 1st trimester, 36.1% in the 2nd trimester, and 51.2% in the 3rd trimester. Drug treatment was given in 12.8% in the 1st trimester, 9.1% in the 2nd trimester, and 15.7% in the 3rd trimester [205].

Controlled trials are very rarely conducted in pregnancy. Sucralfate was significantly more effective than diet and lifestyle interventions in symptomatic remission of heartburn and regurgitation at one month in a randomized controlled trial of 66 pregnant women (90% vs. 43%, $p<0.05$) [203]. Ranitidine was evaluated in a double-blind, placebo-controlled, three-way crossover study in pregnant women (n=20, at least 20 weeks) who did not respond to general measures and antacids. Ranitidine 2x150 mg was effective with respect to symptoms and antacid use [205]. Typically, step-up strategies are recommended in the following order for management of reflux symptoms or GERD in pregnancy: General measures → antacids/alginates/sucralfate → H_2 -RA → PPI [204, 206-211]. These are based on the assumption that antacids have no relevant effects on unborn children and that extensive experience with H_2 -RA, both in clinical practice and in case-control studies, has shown no evidence of increased risk [204, 211, 212]. The exception to this is nizatidine [204]. Alginates are often subsumed in the literature with antacids. A number of uncontrolled studies in pregnancy have shown high efficacy from the patient's perspective with no evidence of relevant side effects [204, 211]. These substances are marketed in various countries, including Germany, for the treatment of heartburn in pregnancy. Sucralfate is not teratogenic in animal studies and is only minimally absorbed. For this reason, despite limited data, the substance is considered safe in pregnancy [204, 211]. PPIs are generally prescribed with great caution in pregnancy. However, a number of prospective and retrospective cohort studies are now available on the question of the safety of PPIs in pregnancy [204, 213]. The incidence of severe anomalies was no greater when a PPI was taken in the 1st trimester than in untreated women. In a meta-analysis of 7 studies (1,530 PPI users and 133,410 controls not taking PPIs), there was no evidence of relevant fetal harm, increased rates of preterm birth or miscarriage [214]. In a large Danish cohort study, PPI exposure during pregnancy or in the 4 weeks before conception was recorded in 5,082 of 840,968 live births. PPI use during the 1st trimester was not associated with relevant malformations [215]. Another large case-control study from Israel with 1,186 PPI exposures during the 1st trimester of pregnancy also found no evidence of an increased rate of malformations; similarly, PPI use in the 3rd trimester did not affect preterm birth, perinatal morbidity and mortality, and low birth weight [216]. However, in the large Danish study, there was a noticeable increase in risk with PPI use in the last 4 weeks before conception - but this did not apply to omeprazole. For this reason, women planning conception who require a PPI should be prescribed omeprazole [217].

The recommendations of the manufacturers of individual drugs with regard to use in pregnancy are: Esomeprazole: only with caution; Lansoprazole: not recommended; Omeprazole: only after careful risk-

benefit assessment; Pantoprazole: contraindication; Rabeprazole: contraindication [213]. Most experience is with omeprazole (www.embrotox.de).

Recommendation 2.15 (new 2022)

If PPI therapy is no longer necessary, treatment should be discontinued. This can be done gradually with the addition of an on-demand medication in case of breakthrough symptoms. (Adults and children)

[Strong recommendation, strong consensus]

Comment

PPIs are often inadequately prescribed for GERD [86, 218]. If the current recommendations of this guideline were adhered to, demand therapy following acute treatment would be recommended in approximately 90% of patients. This means, in essence, that treatment automatically stops when PPIs are no longer needed. In addition, all patients prescribed PPIs for GERD should be regularly reviewed to determine whether there is still a compelling indication for therapy [86].

Approximately 80% of patients with reflux esophagitis experience symptomatic and/or endoscopic recurrence within the first 6-12 months after successful acute therapy. Data on indefinite continuous therapy for GERD with esophagitis are limited. Nearly all controlled therapy studies are limited to 6-12 months [136, 159, 219]. The longest controlled study involving 497 reflux esophagitis patients spanned 5 years [172].

There are - despite the frequency of this disease - only few data on the long-term spontaneous course. The available data suggest that it is a chronic disease in the majority of patients [220]. In patients with "complicated GERD," defined as the presence of structural esophageal damage such as esophagitis, stenosis, and Barrett's metaplasia, long-term persistence is expected in 65% of patients [159]. The global recurrence rate after discontinuation of curative therapy in placebo-controlled trials was 75% (95% CI 69-82%) with a range of variation from 33-100% [159]. In the longest study, conducted in the United States with systematic recording of symptoms and annual endoscopies, the recurrence rate under placebo was 63% within 5 years, or in other words, 37% of patients remained in stable remission and did not require therapy [172].

A large population-based study in Norway has shown that in the long-term course, symptoms of GERD also disappear spontaneously in a substantial proportion of patients [96]. An H. pylori screening study with a ten-year follow-up confirms these data. Of 549 patients with reflux symptoms at the beginning of the study, only 33% complained of such symptoms 10 years later [221]. In particular, weight loss may also contribute to this [96].

An omission trial appears to be possible at low risk in patients with mild esophagitis (Los Angeles A/B), as a large upper-servicing study over 5 years showed that few patients progressed to higher stages of GERD under GP-guided GERD therapy [80]. Also, in a large monocentric long-term study of 2,306 patients in the United States with a mean follow-up of 7.6 years, complications of GERD occurred very rarely with purely symptom-guided management [82]. An alternative is a step-down to demand therapy. In a Cochrane review that included 6 controlled trials with a total of 1,758 patients, a slight increase in

symptoms but a significant decrease in PPI use was seen compared with continuing continuous PPI therapy [222].

In contrast, patients with severe esophagitis (Los Angeles C/D) are likely to have a higher recurrence rate, as there is usually more severe damage to the antireflux barrier [165-167]. Placebo-controlled studies following successful acute therapy with a PPI have shown that nearly all patients with severe esophagitis experience a recurrence within a few weeks [165, 166]. In cases of complicated GERD (bleeding, stenosis), discontinuation of successful long-term therapy is not recommended, as the risk of recurrence appears to be greater than the risk of PPI therapy. This assessment is also based on the observation that the incidence of peptic stenosis decreased significantly after the introduction of PPIs [223].

Placebo-controlled studies have shown that in healthy subjects, abrupt discontinuation of a PPI can lead to an acid rebound triggering dyspeptic symptoms [174, 224]. Symptoms may persist for weeks and are apparently limited to patients who are not infected with Helicobacter pylori. The risk increases with the duration of previous PPI therapy [223]. It is as yet unclear whether acid rebound is also clinically relevant in patients with GERD. In a retrospective evaluation of a controlled therapy study of HP-negative reflux esophagitis patients, there was no evidence of such an effect, but this study approach also has considerable limitations according to the authors' assessment [225]. On the basis of the currently available data, it is reasonable to discontinue therapy gradually in the event of an unsuccessful attempt to stop therapy with rapid recurrence of symptoms. There are data from a controlled study, which showed only a non-significant trend towards a higher success rate [226]. A step-down to an H_2 -RA with the intention of avoiding acid rebound cannot be recommended, as this substance group itself is associated with significant acid hypersecretion after discontinuation [227]. In a prospective, open-label study that included 6,249 patients with dyspepsia and continuous PPI therapy, 75.1% of patients were able to reduce dose or discontinue PPI therapy within 1 year after receiving education and taking an alginate for breakthrough symptoms (40.3%) [228]. However, it is unclear what proportion of reflux patients were in this study.

To date, there is no evidence for the ideal form of discontinuation of PPI therapy [229]. Typically, a stepwise dose reduction is implemented (e.g., double dose to single dose, halving single dose, alternating therapy - e.g., every 2nd day). The optimal length of time between steps has not been studied. A new approach is pH-metric-guided cessation of PPI therapy in patients with typical reflux symptoms or chest pain who do not respond satisfactorily to PPI therapy [230]. In a double-blind study of 100 patients, PPI therapy was discontinued in 34. The strongest predictor was the absence of pathologic acid exposure on wireless pH-metry after at least 7 days of PPI abstinence.

Statement 2.16 (new 2022)

The absolute risk of side effects for PPI is low. In GERD, the benefit outweighs the risk.

[Strong consensus]

Comment

PPIs are used extremely frequently. In recent years, reports of alleged or actual adverse effects have increased. A number of high-quality reviews have critically addressed the risk profile of these drugs based on the scientific data available [86, 171, 213, 218, 231-233].

PPIs inhibit acid production. From this desired effect, at least theoretically, individual undesirable effects such as reduced absorption (e.g., iron, vitamin B12), altered composition of the gut microbiome, and increased rate of gastrointestinal infections can be explained. Interactions with other drugs in liver metabolism are also plausible.

Data on safety risks of PPI come primarily from cohort or case-control studies with associated uncertainties. This type of study does not allow a distinction between association and causality. The occurrence of an event *during* treatment is simply not equivalent to causality. If one takes a closer look at the studies, the calculated risk is consistently in a range that is typical for a bias [233]. Even if one were to accept the risks as given, the absolute risk is almost without exception so low that the benefit of the substances is considerably higher for the given indication. However, there are now randomized controlled trials (comparison of PPI long-term therapy with fundoplicatio) with follow-up of up to 12 years [234]. In neither of these studies were the accused risks observed under PPI. In addition, a study with almost 18,000 patients receiving 40 mg pantoprazole or placebo over 3 years should be highlighted [235]. The aim of this study was to prevent gastrointestinal events during anticoagulation. Pantoprazole and placebo differed only with respect to a slightly increased rate of gastrointestinal infections (119 vs. 90 in 3 years, p=0.04). Notably, there was also no evidence of increased rates of renal disease, dementia, bone fractures, myocardial infarctions, pneumonias, and gastrointestinal malignancies in this study [231, 235]. This study was large enough to demonstrate that the previously suspected adverse effects were of an appropriate magnitude [231].

Very rare side effects and those that occur only after very long use of PPIs cannot be excluded with absolute certainty by the data of the available controlled studies. The side effects dementia, osteoporosis and cancer are particularly frequently addressed and discussed. In the Nurses' Health Study II with 13,864 participants as well as in two large, prospective, population-based twin studies from Denmark, no association was found between PPI use and dementia [236, 237]. In a recent systematic review with meta-analysis that included one randomized and five prospective cohort studies with at least 5 years of follow-up, there was no evidence of dementia as a result of PPI therapy [238]. Since the first publication in 2006, retrospective analyses of databases have been repeatedly published to show an association between PPI use and bone fractures. However, the results were neither coherent nor consistent, and a clear dose-response relationship was also lacking [239]. In a population study in Norway that included 15,017 women and 13,241 men aged 50-85 years, there was no evidence of an increased fracture rate in PPI users during a median follow-up of 5.2 years [240]. A population-based case-control study that included 521 patients with Barrett's esophagus did not demonstrate a higher rate of osteoporotic fractures than age- and sex-matched controls. Also, no effect was found with respect to duration and dosage of PPI therapy [241]. In addition, no accelerated osteoporosis development has been demonstrated to explain an increased fracture propensity [242-244]. In the Canadian Multicenter Osteoporosis Study, PPI users had lower bone density at baseline without a cause being identified. 10-year follow-up data were available for 4,512 subjects and showed no difference between patients or subjects with and without PPI use [244]. In a controlled study, patients on PPI therapy for more than 5

years showed no difference in bone density and strength with comparable individuals without PPI use [243]. In another randomized, placebo-controlled trial over 26 weeks in postmenopausal women, neither esomeprazole nor dexlansoprazole had an effect on bone metabolism [245]. In a recent, large, population-based case-control study, there was no evidence of an increased risk of carcinoma of the digestive tract in PPI users [246].

Overall, it can be stated today that PPIs continue to be drugs with an excellent safety profile. This does not release the prescriber from the obligation to prescribe PPIs only for a given indication, in adequate dosage according to the approval or the state of scientific knowledge, and no longer than necessary - a medical practice that should actually be taken for granted. The current hysteria, which is particularly unsettling for patients who urgently need these medications and also leads physicians to erroneous therapeutic conclusions with potential danger, is frightening and, in view of the data, inappropriate [247-249].

Recommendation 2.17 (new 2022)

If long-term therapy with PPI is necessary, *Helicobacter pylori* diagnostics and therapy should be performed according to the currently valid S2k guideline of the DGVS. (Children and adults)

[Recommendation, strong consensus]

Comment

Reflux symptoms or GERD are not an indication for H. pylori eradication according to the S2k guideline of the DGVS [250]. According to this guideline, H. pylori diagnostics should only be performed if therapeutic consequences are to be drawn from a positive result (germ detection). A systematic review including 16 studies with 1,920 patients showed that long-term PPI therapy resulted in an increased prevalence of ECL cell hyperplasia in HP-positive patients and also significantly increased the risk of atrophy in the corpus compared with HP-negative patients, in addition to an expected moderate hypergastrinemia [251]. However, neuroendocrine tumors or gastric carcinomas were not observed in any of the included studies. Eradication of HP cures gastritis, however, gastric cancer risk remained elevated thereafter with long-term PPI therapy in a population study [252]. An inverse relationship exists epidemiologically between GERD and its complications Barrett's or Barrett's carcinoma and HP, and the effect of PPI is enhanced by HP [253]. However, conclusive evidence that HP eradication in GERD worsens the efficacy of long-term PPI therapy and/or increases the risk of GERD complications is lacking to date [253]. Therefore, the European Helicobacter Study Group recommends in its current consensus report, as does the German guideline, H. pylori eradication prior to long-term PPI therapy to prevent an increase in corpus gastritis and accelerated atrophy development [250, 253].

Special features in childhood

The treatment of gastroesophageal reflux differs from the recommendations of the guideline, especially in premature infants, neonates, infants, and young children. In this regard, reference is made to the American and European guidelines of pediatric gastroenterologists [254].

3 Guideline - Surgical therapy

3.1 Indication and preoperative diagnostics

Recommendation 3.1 (new 2022)

Antireflux surgery should be offered in cases of long-standing confirmed reflux and complicated GERD (e.g., LA grade C/D, peptic stricture).

The indication for antireflux surgery should be evaluated if the patient cannot tolerate long-term medication.

[Recommendation, strong consensus]

Comment:

The therapy of gastroesophageal reflux disease can be conservative or surgical. It has been shown in many cases that patients with documented pathological reflux in the 24h impedance ph-metry measurement and positive reflux symptom correlation can benefit from surgical therapy [255, 256]. Therefore, surgical therapy should be included in the possible treatment options for patients.

The anatomic and functional elements of the antireflux barrier are pathologically altered in patients with severe reflux disease [93, 257-259]. These include, for example, sphincter incompetence, hiatal hernia, and increased number of transient sphincter relaxations.) [11, 260].

With normal sphincter pressure and length as well as an anatomically normal antireflux barrier, reflux can only result from spontaneous sphincter relaxation [93, 257-259].

Sphincter incompetence and/or anatomic changes at the hiatus can result in free reflux, which move backwards into the esophagus through the anatomically and functionally incompetent gastroesophageal junction without other affecting factors. If a lot of free reflux flow back through an anatomically and functionally incompetent antireflux barrier, antireflux surgery should be considered and evaluated using further diagnostics [147].

Children

In children, antireflux surgery should only be considered in case of persistent symptoms due to GERD despite optimal drug therapy or if life-threatening complications occur.

In case of chronic diseases with a significant increased risk of GERD complications (e.g., cystic fibrosis, neurologic diseases with impairment) an indication for antireflux surgery is given [254].

Recommendation 3.2 (modified 2022)

Preoperatively, impedance pH-metry (to prove pathological reflux) should be performed. Symptom correlation should also be documented.

[Strong recommendation, strong consensus]

Comment:

The purpose of preoperative diagnostics is not only to make a diagnosis but also to establish an objective basis for the treatment decision, in particular the indication for surgery. The aim is to optimize the selection of patients who will benefit from anti-reflux surgery. Patient selection includes the detection of pathological acid exposure of the distal esophagus or volume reflux, as symptoms are not sufficiently reliable [261-267].

Especially in refractory reflux patients, preoperative functional examination must be performed in patients to select patients more accurately. In a large study it was shown that the detailed workup of the so-called refractory reflux patients selects 2 different patient groups: A larger group who actually do not suffer from gastroesophageal reflux disease at all and require neither drug nor surgical therapy. The smaller group, however, in whom a pathological reflux could be proven, benefit from surgery and only slightly from a continuation of drug therapy [90].

Children

pH/impedance tests are not reliable for confirming the diagnosis of reflux disease, especially in infants. Healthy infants often have reflux episodes without clinical consequences. There is a weak correlation between abnormal findings and reflux complications [268, 269] .

In children, diagnosis is not always feasible for technical reasons. Especially in infants and young children, the diameter of the probe alone is a limiting factor.

Recommendation 3.3 (modified 2022)

Preoperatively, high-resolution esophageal manometry should be performed to rule out a motility disorder.

[Strong recommendation, strong consensus]

Comment:

Esophageal high-resolution manometry is required for the diagnosis of esophageal motility disorders. Using this method, motility disorders such as achalasia, esophagogastric junction outflow obstruction, hypercontractile motility disorders or lack of esophageal peristalsis are excluded or detected [270-275]. Especially these compromising motility disorders are very important for the preoperative decision-making, as they can influence the choice of the surgical procedure (hemifundoplication according to Toupet or 360° fundoplicatio according to Nissen) or represent a contraindication for antireflux surgery [151, 275, 276].

In addition, evidence of sphincter incompetence as well as evidence of hiatal hernia has some prognostic significance regarding the disease [270, 277].

In children, there is no evidence to support the routine performance of manometry for the diagnosis of GERD. It is only recommended when a motility disorder is suspected. In this case, a high-resolution manometry is recommended [254] and should be sought when planning surgery, if possible.

Recommendation 3.4 (modified 2022)

The following criteria should be evaluated prior to antireflux surgery in adults. (however, not all of them have to apply for the indication of surgery):

- Typical symptoms (medical history)
- Length, type and therapy of the reflux history (medical history)
- Positive PPI response
- Change in PPI therapy (double standard dose PPI, PPI change, dose splitting).
- Presence of hiatal hernia (endoscopy, radiography, high-resolution manometry).
- Incompetent antireflux barrier (high-resolution manometry).
- Pathological acid exposure with symptom correlation (pH-metry, impedance-pH-metry, SAP Symptom-Association-Probability).
- Change in the quality of life

[Strong recommendation, strong consensus]

Comment:

In general, drug therapy, especially with proton pump inhibitors, is very effective, and with dose increase, dose splitting, and different PPI, various options for conservative therapy are available. Nevertheless, there is a proportion of reflux patients who do not benefit or do not benefit sufficiently from conservative therapy. If patients are well selected, antireflux surgery may thus be a better alternative [90]. The above-mentioned criteria should be used for theselection of therapy refractory patients.

In several studies, these criteria have either been specifically reviewed for their relevance, or study results allow conclusions to be drawn regarding the usability of these criteria [80, 277-286]. A similar consensus was also reached internationally: in 2019, the Icarus Guidelines were published with similar recommendations for the selection of suitable patients for surgical treatment [287].

When these criteria are applied, antireflux surgery has been shown to improve the quality of life of patients with gastroesophageal reflux disease [278, 281, 282].

If patients fullfill the indication criteria, antireflux surgery may be considered. This is usually the case if, despite adequate PPI therapy (adjusted dosage, change of dosage, splitting and correct intake), the symptoms cannot be completely controlled, which results in a reduced quality of life. In addition, younger patients in particular do not want to be on medication permanently, so that antireflux surgery is an alternative in these cases as well; however, well-medicated patients should be informed that new postoperative symptoms may occasionally occur after antireflux surgery and that the success of surgery does not always last a lifetime. If PPI side effects or intolerances make long-term use impossible, antireflux surgery is also warranted [278, 281, 282, 284-287].

This is true for children [254, 288, 289] as well as for adults.

3.2 Operative procedures

Recommendation 3.5 (new 2022)

Laparoscopic fundoplication should be performed as first-line surgical therapy. The procedure is effective and has only few complications.

[Strong recommendation, strong consensus]

Comment:

Laparoscopic fundoplication is a minimally invasive operation with low morbidity and very low mortality. The patient should be informed that laparoscopic fundoplication has a morbidity rate of less than 10%, a complication rate of less than 5%, and a lethality rate of less than 0.2% in experienced centers [290, 291]. Patients with known risk factors and relevant secondary diseases should be evaluated carefully regarding their risk,and the indication for antireflux surgery should be adjusted accordingly [290, 292, 293].

In patients with an underlying mental or psychiatric illness, the success of antireflux surgery may be limited. Compared to the preoperative situation, however, an improvement can still be achieved. A detailed preoperative diagnosis with evidence of an objectifiable gastroesophageal reflux disease is essential in these cases [149, 294-296].

This is also true for children, although underlying neurological diseases are more common here.

If the indication criteria are met, surgery indication should also be considered in patients with nonerosive gastroesophageal reflux disease (NERD) or hypersensitive esophagus. The results of antireflux surgery in erosive and nonerosive esophagitis were comparable in both subjective and objective parameters [123, 297].

The question of comparing drug and surgical therapy for gastroesophageal reflux disease has been the subject of controversial debate between gastroenterologists and surgeons, although in recent years the focus has increasingly been on and the procedures do not compete with each other. Rather, surgical treatment is an alternative for selected patients [287, 298].

There are four randomized trials for direct comparison of drug and surgical therapy [80, 284-286]. In Europe, the results of the Lotus study, a large randomized study, were published after 5 years. [286]. The study concludes that the effectiveness of both PPI therapy and laparoscopic Nissen fundoplication is very good in a follow-up of up to 5 years. The good success of surgery is somewhat limited by the development of long-term problems as well as recurrences; therefore, the failure rate after five years is slightly higher in the surgical therapy group, but does not reach significance. It should be noted, that a major inclusion criterion for the study was successful response to esomeprazole therapy. Thus, only patients with a positive response were admitted and therapy failures were not included at all. This represents a significant bias for drug therapy.

Three other randomized trials (follow-up 3 to 7 years) reached a different conclusion and showed that patients who underwent laparoscopic antireflux surgery using Nissen fundoplication were at an advantage over treatment with PPI in terms of postoperative reflux symptoms and quality of life [284, 285, 299]. They had a significantly better quality of life and symptom control was also better compared with conservative therapy. Thus, laparoscopic fundoplication is a very good alternative for the treatment of gastroesophageal reflux disease.

These randomized prospective studies were all conducted in adult populations. There are no randomized controlled trials on this topicin children, only retrospective case series [254].

Laparoscopic fundoplication is now the gold standard and its advantages over the open variant have been demonstrated in several randomized trials [300-302].

The optimal shape of the cuff, whether full cuff (Nissen) or half cuff (Toupet), is the subject of lively debate among experts and has been investigated in a total of 13 randomized controlled trials, numerous large case-control studies from major centers, and several meta-analyses in recent years with overall controversial conclusions [278, 282, 303-328].

In centers with limited experience with the Nissen fundoplication, the posterior partial cuff according to Toupet, which has fewer side effects, should be preferred, asthe Nissen cuff may have more side effects and the reoperation rate may be higher [303, 306-310, 313-318, 322, 323, 329]. In experienced centers with the Nissen full cuff, this version should be preferred due to its good long-term effectiveness [278, 282, 319-321, 324-328] .

Recommendation 3.6 (new 2022)

Surgical alternatives to fundoplication, such as magnetic sphincter augmentation, have shown promising results in current studies, and may be considered if the indication is precise.

[Recommendation Open, Strong Consensus]

Comment:

In patients with confirmed reflux disease and only a small hiatal hernia, the performance of alternative surgical procedures (e.g., MSA LINX) or endoscopic procedures may be considered despite the current lack of evidence. However, this should be performed either in the context of studies and/or at selected centers [330-333].

Mobilization of the esophagus up into the mediastinum and reconstruction of the anatomy with localization of the distal esophagus into the abdomen should be performed in any antireflux surgery [334].Resection of the hernia sac is also required for larger hernias.

Adequate narrowing of the hiatus should be performed in every antireflux operation with hiatal hernia [335-338]. Hiatoplasty can be performed both anteriorly and posteriorly [339].

Recommendation 3.7 (new 2022)

Reinforcement of the hiatus with foreign material should not be performed routinely. The indication for mesh reinforcement of the hiatus should therefore be critically reviewed and based on the defect size of the hiatus.

[Strong recommendation, strong consensus]

Comment:

The current data on mesh reinforcement of the hiatus remains controversial and does not allow a clear recommendation. Most studies regarding prosthetic hiatal closure include patients with large hiatal hernias (radiologically > 5 cm) or paraesophageal hernias. Patients with symptomatic reflux disease and small hiatal hernia were not included [340-346].

On the one hand, benefits of mesh reinforcement have been demonstrated with respect to hiatal hernia recurrence rate, but on the other hand, the risk of developing a severe complication with subsequent need for resection is not negligible [347-352].

Due to the low evidence level of currently available data, the indication for mesh reinforcement of hiatoplasty must be critically evaluated. Regarding postoperative recurrence rates, available studies show advantages of prosthetic hiatoplasty in some studies, but there is a lack of a standardized approach e.g. regarding mesh shape, mesh material as well as mesh positioning. The indication for mesh implantation should be based on the size of the hernia, if at all, and should be verified in studies. In children, foreign material is generally only used in exceptional situations.

Recommendation 3.8 (new 2022)

Symptomatic paraesophageal hiatal hernia and up-side-down stomach should be treated surgically.

[Recommendation, strong consensus]

Comment:

The term paraesophageal hernia is very often used in the literature for a collection of different entities such as large mixed hernia, thoracic stomach, true paraesophageal hernia and up-side-down stomach. The difference between true paraesophageal hernia and up-side-down stomach on the one hand and large mixed hernia or thoracic stomach on the other hand is the anatomical weakness at the phrenicoesophageal membrane in the hiatus. In large mixed hernia (or thoracic stomach), primarily circular weakness of the membrane develops so that the esophagus and cardia gradually dislocate cranially into the mediastinum and a "short esophagus" (abdominal esophagus cannot be mobilized into the abdomen without tension) develops. In true paraesophageal hernia or up-side-down stomach, a weak spot develops locally in the circumference of the phrenicoesophageal membrane so that herniation of the stomach is localized and the cardia remains at the hiatal level. This explains the flipping (up-side-down) of the stomach through the primary non-circumferential gap. Since in both cases the cardia and the hiatus region must be completely dissected to allow anatomic reconstruction, the likelihood of subsequent pathologic reflux is high and antireflux measures should be considered [334, 353-356].

Collis plastic

In the presence of "short esophagus", adequate extension of the esophagus through the gastric fundus (collis-plasty) should be performed in adults during laparoscopic fundoplication. It may contribute to the success of therapy and to the reduction of the recurrence rate after surgery of large hernias [357-361].

3.3 Recurrences

Recommendation 3.9 (new 2022)

Reflux recurrences without diagnostically proven anatomic-morphologic complications should initially be treated again with PPI.

[Recommendation, strong consensus]

Comment:

Basically, one can speak of a reflux recurrence if the previous symptoms of reflux persist or recur to the same extent, or if new symptoms such as dysphagia, vomiting and pain occur. The documentation of quality of life (general and/or specific) before and after surgery is an important criterion to determine the quality of outcome and recurrence [278, 282, 294, 362].

After Nissen fundoplication, more than 80% of patients still have good symptom control after 15 years [363]. A large retrospective study of more than 13.000 patients after fundoplication showed a recurrence rate of 5.2% after 5 years and 6.9% after 10 years. Younger patients and women were more frequently affected [364].

However, it should be clearly stated here, and there are good data for this, which should not be concealed, that up to 30% of patients will need the PPI again during their lifetime after surgery.

Retrospective studies in large pediatric collectives have shown recurrence rates ranging from 4.6 to 12.2% [302, 365].

Pure reflux recurrences should be treated with PPI. In individual cases, reflux diagnostics should be repeated. It is important to follow up any unusual symptoms other than heartburn and acid regurgitation with detailed diagnostics and questioning to determine the exact cause, if possible, and to understand the underlying mechanism of the symptoms [278, 282, 294, 321, 366, 367].

Recommendation 3.10 (modified 2022)

In cases of dysphagia or pain after antireflux surgery with a significant reduction in quality of life, a rapid and clarifying diagnosis should be made.

[Recommendation, strong consensus]

Comment:

Dysphagia and pain, sometimes even with massive limitations in quality of life as well as food and fluid intake, require rapid clarification and, if necessary, early revision surgery in an experienced center. Laparoscopic and open revision surgery after fundoplication are feasible and safe, but have a longer operative time, a higher complication rate, and incur higher costs [368-375]. Since the likelihood of a complex, high-risk procedure up to major resections of the esophagus or stomach increases with the number of re-operations, it seems reasonable to have the first revision procedure performed in an experienced center with appropriate surgical expertise as well.

Recommendation 3.11 (modified 2022)

The therapeutic decision for revision surgery should be made on an interdisciplinary basis.

[Strong recommendation, strong consensus]

This procedure should be performed by a specialized antireflux surgeon.

[Strong recommendation, consensus]

Recurrent surgeries are often technically complex and difficult [376, 377]and the success rates are somewhat lower compared to the initial operation [364]. Before surgery, a detailed diagnosis should be made. This includes at least high-resolution manometry or an X-ray swallow or (bread) barium swallow. With the required findings, an interdisciplinary discussion with gastroenterologists and visceral surgeons should take place, which is best performed in a reflux center [378, 379].

4 Guideline - Barrett's esophagus

4.1 Endoscopic and histological diagnostic confirmation

Statement 4.1 (audited 2022)

The diagnosis of Barrett's esophagus is made histologically by detection of specialized intestinal and goblet cell metaplastic cylinder epithelium when endoscopic-macroscopic suspicion is present.

[Strong consensus]

Comment:

Specialized intestinal metaplastic cylinder epithelium is characterized by goblet cells ("intestinal metaplasia"). These are absent in corpus- or fundus-type cylinder epithelium, which may also be present in cylinder epithelium-lined esophagus. The extent to which the diagnosis of Barrett's esophagus requires the detection of metaplastic cylinder epithelium with goblet cells in the sense of intestinal metaplasia or whether cylinder epithelium without goblet cells is sufficient has been under discussion for several years.

In retrospective studies from England, the risk of carcinoma was the same for a cylinder epithelium-lined distal esophagus with and without goblet cells [380, 381]. This has led the British Society of Gastroenterology to designate metaplastic cylinder epithelium without goblet cells as Barrett's esophagus as early as 2005 [382].

This approach is problematic biopsies from the Z-line and the question of an ultra-short Barrett esophagus, because the there is only evidence for the metaplastic nature of the cylinder epithelium at the esophagocardial junctional zone and thus changes of an inflammation of the cardiac mucosa can rarely be delineated [383, 384].

Prospective randomized trials are lacking for Barrett's esophagus without evidence of intestinal metaplasia, so the benefit of regular surveillance of patients with cylinder epithelium without goblet cells has not been established with certainty. Substantial data supporting regular surveillance of only patients with histologically proven intestinal metaplasia was contributed by a 2008 meta-analysis of carcinoma incidence in Barrett's esophagus [385]. In this publication, when only patients with intestinal metaplasia were considered, the incidence of carcinoma was 4.7/1000 person-years.

Still, the detection of intestinal metaplasia must be considered the standard for the diagnosis of Barrett esophagus as long as the carcinoma risk for patients with a cylinder epithelium without goblet cells is not proven with certainty.

Recommendation 4.2 (reviewed 2022)

If gastric epithelium is detected (also known as Barrett's with the addition of gastric metaplasia according to Montreal classification), a control EGD should be performed within one year.

[Recommendation, strong consensus]

Comment:

The probability of detecting intestinal metaplasia in a cylinder epithelium-lined esophagus depends on the length of the endoscopically suspicious segment and the number of biopsies obtained [381]. If a patient is clinically endoscopically suspected of having Barrett's esophagus but intestinal metaplasia is not histologically detectable, a control biopsy can provide goblet cell evidence and compensate for any sampling error in the initial biopsy. Furthermore, carcinomas can in principle also arise in surrounding cylinder epithelial metaplasia of the cardia or fundus type, as was shown in a study of smaller tumors in mucosectomy specimens [386]. Two studies comparing carcinoma development in goblet cell-containing and goblet cell-free gastric epithelium describe carcinoma development only in the presence of goblet cells [387, 388].

Recommendation 4.3 (modified 2022)

Endoscopic description should be according to the Prague classification, which includes circular extension of cylinder metaplasia proximally into the esophagus (C) and maximal extension of cylinder epithelial metaplasia (M).

[Strong recommendation, strong consensus]

Suspect lesions should be described using the Paris classification.

[Recommendation, strong consensus]

In the case of suspicious lesions, the localization (distance from the tooth row in centimeters and circular localization based on the time) and the size should be indicated in the findings.

[Strong recommendation, strong consensus]

Table 7: Paris Classification

Classification	Meaning	Description
Type 0-I	raised or polypous/polypoidal forms	0-Ip polypoid/polypous-sided 0-Is polypoid/polypoid-sessile, broad-based
Type 0-II	shallow or superficial forms	0-IIa flat-raised 0-IIb completely flat 0-IIc superficially sunken
Type 0-III	sunken/ulcerated form	

Comment:

Detection of specialized cylinder epithelial metaplasia in the distal esophagus is associated with an increased risk of carcinoma for the patient. Previously, an arbitrarily chosen length of 3 cm was used to distinguish short (< 3 cm) from long (≥ 3 cm) Barrett's esophagus. Specifying the extent of intestinal metaplastic cylinder epithelium is important because studies have shown that patients with long-Barrett's

esophagus have a higher risk of carcinoma than those with short-Barrett's esophagus [389-391]. The Prague classification includes both circumferential (C) and maximal extent (M) of cylinder epithelial metaplasia [392]. Because there is excellent interobserver agreement at an extension of at least 1 cm, this classification should continue to be used and the diagnosis of Barrett's esophagus should be made only at a length of 1 cm.

The Paris classification is an internationally accepted and validated classification for the macroscopic description of early neoplastic lesions. The Paris classification divides into raised (type I), flat (type IIa, b, c), and ulcerated (type III) neoplasms. Different macroscopic types are associated with an increased risk of submucosal infiltration and for this reason are also prognostically relevant [393, 394]. The European guidelines for quality in endoscopy of the upper gastrointestinal tract require the Prague classification, the localization and in case of a suspicious lesion the description according to the Paris classification and the size of the lesion as a minimum standard in an endoscopic report [395].

Recommendation 4.4 (reviewed 2022)

The gastroesophageal junction should be determined endoscopically and corresponds to the proximal end of the gastric folds without air insufflation or peristalsis.

[Strong recommendation, strong consensus]

Comment:

Analogous to the 2005 and 2015 guideline, the gastroesophageal junction is determined endoscopically. Due to the lack of alternative landmarks, the proximal gastric folds determine the gastroesophageal junction. Difficulties arise with strong peristalsis, poorly sedated patients, or large axial hiatal hernias [396].

Recommendation 4.5 (new 2022)

In Barrett's esophagus, drug therapy should be based on symptoms and concomitant peptic lesions (reflux esophagitis, peptic stricture). Therapy to prevent dysplasia has not been established.

[Recommendation, strong consensus]

Comment:

The current evidence on chemoprevention of malignant degeneration of Barrett's esophagus is insufficient for a recommendation. For this reason, even in the presence of Barrett's esophagus, only symptom-based drug therapy should be used.

PPI, NSAID and statins are currently the most promising agents for chemoprevention of neoplastic progression of Barrett's esophagus. PPIs are commonly recommended in patients with Barrett's esophagus and reflux symptoms. Whether this results in a risk reduction with respect to the development of HGD or adenocarcinoma has not been fully established. In a meta-analysis of 2813 patients with Barrett's esophagus, PPI use reduced the risk of adenocarcinoma development by 71% (OR 0.29, 95% CI 0.12-0.79) [397]. Contradictory to this were the results of a population-based study from Denmark. Here, no protective effect could be shown in 9833 patients with Barrett's esophagus.

Both aspirin and proton pump inhibitors appear to be effective in preventing dysplasia in patients with Barrett's esophagus. Several ex vivo and in vitro studies have shown that gastric acid causes DNA damage and may have proliferative and antiapoptotic effects. Thus, a carcinoma preventive effect of acid suppressive therapy was indirectly concluded [398, 399]. In a large randomized and highly published study (AspECT-Trial), a total of [400] a total of 2557 patients with Barrett's esophagus larger than 1 cm were followed with either 20 mg esomeprazole, 2 x 40 mg esomeprazole, plus each with or without aspirin 300 mg for at least eight years. Here, the combination of a high dose of esomeprazole with aspirin had an effect on overall mortality (time ratio (TR) 1.36, 95% CI 1.01-1.82) compared with low-dose esomeprazole and no aspirin. However, no effect on carcinogenesis was demonstrated. Side effects occurred in one percent of patients on therapy. However, it must be taken into account that an effect of the therapy appears after five years at the earliest. The influence on overall survival is difficult to interpret in this context.

Statins also appear to have a chemopreventive effect. In a case-control study of 303 Barrett's patients and 909 controls, statin use was associated with a 43% risk reduction for developing Barrett's (OR 0.57, 95% CI 0.38-0.87) [401]. Another case-control study also demonstrated a protective effect of statins on adenocarcinoma development. In 311 patients with Barrett's adenocarcinoma and 856 matched controls, there was a 35% risk reduction ((OR 0.65, 95% CI 0.47-0.91) [402]. However, prospective controlled studies demonstrating such a protective effect do not yet exist.

In summary, no general recommendation for chemoprevention can be made at this time.

Recommendation 4.6 (modified 2022)

In case of endoscopic suspicion or already confirmed Barrett's esophagus, an extensive inspection of Barrett's mucosa should be performed followed by targeted biopsy of all suspicious areas and subsequent 4-quadrant biopsy every 1-2 cm.

Suspect areas should be preserved separately and examined histopathologically. Otherwise, there is no need for separate preservation of the biopsies.

[Strong recommendation, strong consensus]

Comment:

Despite all available modern imaging techniques, 4-quadrant biopsy still appears necessary after careful endoscopic evaluation. However, an extensive inspection of the Barrett's mucosa with high-resolution videoendoscopes should be performed first. For this, approximately 1 minute of inspection time should be used for each centimeter of Barrett's length. In a retrospective study it was shown that significantly more neoplastic areas (HGIN and early carcinomas) can be detected [403]. This recommendation has found its way into the guidelines of the ESGE on the quality of endoscopy of the upper GI tract [395]. Endoscopically suspicious areas should first be specifically biopsied and also separately preserved. This seems to be useful to allow a better localization of the neoplastic area prior to possible mucosectomy. The localization should be the height from the dentition and according to a clock face

(e.g. 34 cm 2.00 o'clock). If significant inflammatory changes of Barrett's esophagus are present, 4 weeks of PPI therapy should be given prior to evaluation and biopsy collection to avoid endoscopic and histopathologic misclassification.

Separate preservation of individual 4-quadrant biopsies does not appear to be necessary because, on the one hand, localization is very difficult to reproduce here and, on the other hand, ablation of the entire Barrett segment should also be performed if dysplasia is not visible endoscopically (see endoscopic therapy) [404-406].

Recommendation 4.7 (modified 2022)

Chromoendoscopy (indigocarmine, acetic acid) and/or computer-assisted digital (filter) techniques should additionally be used as part of a surveillance endoscopy.

[Recommendation, strong consensus]

Comment:

Chromoendoscopy after application of methylene blue [407] or crystal violet [408] is no longer in use due to potentially toxic and mutagenic side effects. What can be used is the local application of acetic acid 1.5% [409] or indigo carmine [410]. Although this does not stain the mucosa, contrast enhancement occurs to better visualize the gyration of the mucosa typical of Barrett's or irregularities in dysplasia. Three other studies with evidence level 2a clearly suggest that both simple spray techniques and existing technical procedures for more accurate/better contrasted mucosal surface viewing improve the detection of early neoplasia in high-risk patients. For example, the work of Coletta et al. (2016) showed [411] in the form of a meta-analysis (13 studies) shows once again that simple acetic acid irrigation in Barrett's esophagus-but only in conjunction with histology-achieves this goal. Thus, this technique achieves a sensitivity for HGD and early carcinoma (Barrett's) of 92% with a specificity of 96%. For the detection of non-dysplastic, pure Barrett's metaplasia, these values were 96% and 69% (specificity without histology). Therefore, acetic acid-positive findings should always be combined with histology due to specificity limitations.

As an alternative to chromoendoscopy, there are optical methods based on a change in the light spectrum, thus enabling more or less digital chromoendoscopy at the "push of a button". These methods also allow contrast enhancement and, in particular, better visualization of vascular structures. The work of Qumseya BJ et al. (2013) [412] is a meta-analysis,which included 11 RCTs. It investigated whether classical and virtual chromo-endoscopy techniques can improve the results of white light endoscopy in detecting esophageal neoplasia in Barrett's esophagus. In this regard, classic chromoendoscopy and virtual procedures improved biopsy-reviewed detection rates of HG-IEN and early carcinoma by up to 34% (CI 20-56%, $p < 0.0001$). Subgroup analyses also showed that the virtual chromoendoscopy procedures in particular allowed this diagnostic improvement (evidence level 2a).

4.2 Therapy and follow-up

Recommendation 4.8 (reviewed 2022)

Endoscopic therapy/ ablation of non-dysplastic Barrett's mucosa should not be performed.

[Strong recommendation, strong consensus] *(Decide Wisely).*

Comment:

The risk of progression of non-neoplastic Barrett's esophagus to high-grade dyplasia or adenocarcinoma is extremely low, reported in recent studies to be 0.12 to 0.33 per year [83, 413]. This low risk is offset by the risk of complications associated with ablative therapy. Even in the context of radiofrequency ablation therapy, the method with the lowest complication rate, relevant complications such as stenosis occur in 6.5% to 9% [414, 415]. Moreover, the prerequisite for ablation therapy of non-neoplastic Barrett's mucosa would be a very high rate of complete ablations combined with an extremely low risk of recurrence. Especially recent data on radiofrequency ablation suggest that the long-term success of radiofrequency ablation is unsatisfactory, so that complete ablation cannot be guaranteed in the majority of cases.

Another important argument against prophylactic ablation of non-neoplastic Barrett's mucosa is the high cost and the need for lifelong monitoring despite therapy. Long-term data supporting ablation are not available.

Recommendation 4.9 (modified 2022)

If low-grade dysplasia (LGD) is detected on quadrant biopsy, a control EGD should be performed in 2-3 months to reliably exclude the presence of a visible lesion. In case of a visible lesion, endoscopic resection should be performed.

[Strong recommendation, strong consensus]

Comment: Confirmed low-grade dysplasia is a relevant disease with a high rate of progression. The diagnosis of low-grade dysplasia (LGD) must always be verified by an experienced pathologist with a special interest in Barrett's esophagus, as it is often a misdiagnosis [416-419]. Two studies by the Amsterdam Working Group were able to impressively demonstrate that the diagnosis of LGD made by non-expert pathologists is wrong in most cases (73-85%) [418, 419]. In the majority of cases it was the misinterpretation of inflammatory and regenerative changes. Interestingly, progression in the long-term course occurred only in patients with true LGD. The importance of expert-pathologist concordance was also demonstrated in another study by the study group: In a study of 255 patients with LGD, progression to HGD and Barrett's adenocarcinoma was seen in 18% of patients after 42 months of follow-up. This was significantly higher in patients who had concordance in the diagnosis of LGD from 3 expert pathologists (odds ratio 47.14; 95% confidence interval, 13.10-169.70).

These figures illustrate the relevance of the diagnosis of LGD by experienced pathologists. Furthermore, they show that LGD is a relevant diagnosis that requires either close follow-up or endoscopic ablation by RFA. Since LGD in association with a visible lesion is often already HGD or adenocarcinoma, endoscopic resection with diagnostic and therapeutic intent should always be performed.

Recommendation 4.10 (modified 2022)

If endoscopically nonlocalizable low-grade dysplasia is detected in Barrett's esophagus and confirmed by a second experienced pathologist, radiofrequency ablation should be performed to prevent progression. Alternatively, endoscopic follow-up can be performed at 6 months and then annually.

[Recommendation/recommendation open, strong consensus]

Comment:

As described earlier, LGD is a diagnosis with a high rate of progression [83, 418, 420-422]. For this reason, it is important to have a short-term and careful control endoscopy after 3-4 months with biopsy of all visible lesions followed by 4-quadrant biopsy every 1-2cm. If LGD is diagnosed again, ablation of Barrett's esophagus by RFA should be performed. Alternatively, a follow-up LGD can be performed after 6 months.

Radiofrequency ablation (RFA) of barrette epithelium with LGD is safe and effective. A meta-analysis of 19 studies with 2746 patients could show that there is a significant reduction of progression of LGD by RFA compared to surveillance (RR 0.14% 95% CI: 0.04-0.45; P=0.001). On the other hand, regular surveillance endoscopies every 6 months are an alternative to RFA, as this can detect progression in time and lead to endoscopic therapy. For example, in the SURF study, no endoscopically untreatable Barrett's adenocarcinoma developed.

Long-term data from the SURF trial also demonstrate the effectiveness of RFA in patients with LGD after a median follow-up of 73 months [423]. The absolute risk of developing HGD and Barrett's carcinoma was reduced by 32.4%. The Number Needed to Treat was 3.1. Complete remission of Barrett's esophagus and LGD was achieved in 90% of patients by RFA. Recurrence of LGIN occurred in 3/75 (4%) patients.

Recommendation 4.11 (reviewed 2022)

If there is evidence of high-grade dysplasia or mucosal carcinoma in Barrett's esophagus, endoscopic resection should be performed, as this provides staging of the lesion with the question of deep infiltration in addition to therapy.

[Strong recommendation, strong consensus]

Comment:

The presence of HGD or mucosal adenocarcinoma in Barrett's esophagus is a clear indication for therapy. The therapy of choice is endoscopic resection (ER), using either multiband ER or ESD [424-430]. Numerous cohort studies have shown ER to be an effective and safe therapy with a similar curation rate to esophageal resection at a lower complication rate [431-438]. ER can achieve both complete removal of the neoplastic lesion and accurate histologic staging. By carefully processing the resectate, the pathologist can make an accurate assessment of the depth of infiltration, the degree of differentiation, and the possible presence of lymphatic and blood vessel infiltration. Thus, risk stratification can be performed so that after performing ER, the course can be set either toward surgical therapy or toward continuation of endoscopic therapy. Indications for esophageal resection are:

1. Lymphatic vessel invasion (L1) or vein invasion (V1)
2. Infiltration of the upper third of the submucosa (T1sm1) and presence of one of the following risk factors: size >20 mm, poor degree of differentiation (G3), L1, V1
3. deep infiltration into the submucosa (≥500 µm)
4. Tumor remnant at the basal resection margin (R1 basal) [439-441].

If a poor degree of differentiation is present in mucosal Barrett's carcinoma, the risk of recurrence is increased, but according to available data it is not a risk factor for lymph node metastases. In case of a not certainly complete ER or "piece meal" ER of a neoplastic lesion with evidence of tumor at the lateral resection margin (R1 lateral), no surgical therapy is initially indicated. During the next follow-up, a careful evaluation of the resection site and, if necessary, resection in the presence of residual dysplasia is indicated [426, 429, 434].

ER is most commonly performed using a suction-and-cutting technique with the aid of either a ligation set (ER-L) or a cap (ER-C). With these techniques, neoplastic lesions up to 15 mm in size can usually be completely resected. For larger neoplastic lesions, resection is performed using a "piece meal" technique.

Endoscopic submucosal dissection can be used for en bloc resection of larger lesions. With this technique, R0 resection, which is desirable from an oncologic point of view, can be performed regardless of lesion size. However, little data exist to date for Barrett's carcinoma. In a prospective randomized study, piece-meal ER was compared with ESD in 40 patients with early Barrett's carcinoma [442]. This showed no advantage for ESD compared to conventional ER in patients with lesions of approximately 15mm.

Prior to endoscopic therapy, endosonography is usually not useful for evaluating the depth of infiltration of early carcinoma. In numerous studies and meta-analyses, endoscopic ultrasound (EUS) was shown to be too inaccurate for the assessment of infiltration depth in T1 Barrett's adenocarcinoma [443-446]. Furthermore, the performance of pretherapeutic EUS very rarely has an impact on the further therapeutic approach. For this reason, the use of EUS in early Barrett's neoplasms is generally not recommended.

Recommendation 4.12 (modified 2022)

In the case of a primarily invisible HGD, a localization attempt should be made in an endoscopic department with experience in the diagnosis and therapy of early carcinomas of the upper GI tract.

[Recommendation, strong consensus]

Comment:

If HGD is diagnosed during a 4-quadrant biopsy of a macroscopically nonsuspicious Barrett's esophagus, a new careful endoscopic examination with a high-resolution endoscope should be performed in a center with experience in the diagnosis and therapy of early carcinomas of the upper gastrointestinal tract [447-449]. According to a study from the Netherlands, the detection rate of Barrett's neoplasia was 60% in non-expert centers and 87% in expert centers [449]. An expert center is usually

defined as a clinic with at least 20 endoscopically treated patients with early upper GI tract carcinoma [450]. In case of macroscopically suspicious lesions, diagnostic ER is indicated.
Uncritical ablation of the barrett esophagus by RFA carries the risk of undertreatment of an overlooked and more advanced neoplastic lesion. This would lead to delay of curative therapy and possibly be associated with a worsening of the long-term prognosis.

Recommendation 4.13a (modified 2022)
Ablative therapies should not be used in the primary treatment of HGD and mucosal carcinomas because histologic staging is not performed.

[Strong recommendation, strong consensus]

Recommendation 4.13b (modified 2022)
An endoscopically invisible but histologically confirmed HGD and/or adenocarcinoma should be presented for secondary evaluation in an endoscopic department with experience in the diagnosis and treatment of early carcinomas of the upper GI tract.

[Recommendation, strong consensus]

Comment:
All ablative therapies, regardless of the method, have the disadvantage of destroying the dysplasia and thus not allowing histologic staging. Since no procedure exists that can pretherapeutically detect all of the above risk factors that would potentially lead to the recommendation of esophageal resection, ablative procedures should not be performed as the first procedure for HGD and adenocarcinoma [450, 451]. An exception is the presence of a histologically confirmed HGD by the second reviewing pathologist and the repeated negative attempt of localization by an experienced center with high expertise in endoscopic diagnosis and therapy of early dysplasias in the upper GI tract [449, 451, 452]. In such a case, the likelihood of more advanced dysplasia is very low, so there is little risk of undertreatment. In this case, RFA is the therapy of choice [452, 453]. Alternatively, in cases of tongue-shaped Barrett's esophagus, complete ER of Barrett's tongue can be performed [435, 454]. This would ensure both sufficient therapy and histologic correlation with staging.

Recommendation 4.14 (new 2022)
The goal of ablation is complete removal of all Barrett's mucosa in the tubular esophagus and at the Z-line. This should be demonstrated bioptically using quadrant biopsies.

[Recommendation, Strong Consensus]

Comment:
After successful resection of all visible dysplasia in Barrett's esophagus, the residual non-neoplastic Barrett's esophagus should be ablated.

After successful ER of HGD and early Barrett's adenocarcinoma, recurrence and metachronous dysplasia occurs up to 30% if Barrett's mucosa is not completely ablated. In a meta-analysis of 18 studies with 3802 patients A complete ablation of Barrett's mucosa succeeded in 78% of patients, and a complete remission of dysplasia was achieved in 91% [455]. Recurrence of Barrett's mucosa was observed in 13% of patients. The most common complication was esophageal stenosis in 5% of cases. In a large multicenter prospective European cohort study, the two-stage approach with ER followed by RFA was investigated in 132 patients with HGIN and early Barrett's adenocarcinoma: In the per-protocol analysis, complete remission of dysplasia was achieved in 98% and of Barrett's mucosa in 93% [427].
Several procedures are available for ablation. The ablation procedure with the best evidence is radiofrequency ablation. Here, a large number of prospective and partly randomized studies exist that demonstrate the efficacy and safety of RFA. A balloon catheter exists that can be used to ablate longer circular segments of Barrett's disease. It is important to note that with the currently available self-measuring balloon catheter (Barrx™-360 Express RFA Balloon Catheter), after the first ablation procedure, the ablated mucosa must be cleaned with a soft attachment cap and irrigation before the second ablation step is performed. Two ablations without the intermediate step of cleaning results in a significantly increased stenosis rate. When using the focal catheter (Barrx™-90), a 3-time ablation without an intermediate step can also be performed as an alternative to the standard variant with two ablations, cleaning followed by another two ablations. In addition to the ablation balloon, focal ablation catheters also exist and are used primarily for ablation of tongue-shaped or island-shaped Barrett's areas. When using these focal ablation catheters (especially HALO 90), ablation of the Neo-Z line should always be performed, since residual Barrett's mucosa is often found there and neoplastic recurrences are most frequent here.

Another ablation procedure available is Argon-Plasma-Coagulation (APC) . This APC can be used conventionally without prior mucosal injection or as a hybrid APC with injection [456]. In a multicenter prospective randomized study from the UK, RFA and APC were equally effective and had comparable complication rates (stenosis 8%). RFA was significantly more expensive on a patient basis with an additional cost of 27500US$ compared to APC [457].
Cryotherapy has been successfully used as an alternative ablation procedure in studies in the USA and also in Europe, but is not yet available and approved in Europe [458-460].
Complete radical ER of the entire Barrett's esophagus is also an option for complete removal of the dysplasia and Barrett's mucosa. However, this procedure is associated with an intolerable high stenosis rate of up to 88% [454, 461, 462]. In a meta-analysis of 20 studies, focal ER followed by RFA was shown to be equally effective as complete ER of Barrett's mucosa, but significantly safer [462].
The goal of ablation should represent complete removal of all cylinder epithelial metaplasia in the tubular esophagus. Complete removal should be confirmed by high-resolution videoendoscopy and chromoendoscopy. In addition, 4-quadrant biopsies of the cardia (defined as the area at the proximal end of the gastric/cardiac folds) should be performed to exclude residual Barrett's mucosa.
Ablation therapies should be performed every 2-3 months. Each endoscopic therapy should be followed by high-dose therapy with proton pump inhibitors (2x1 standard dose/day) until the patient's next presentation. Additionally, addition of H2 blockers, alginates or sucralfate may facilitate healing.

Continuation of ablation should only be performed in case of complete healing of the ablation area after previous therapy. Inflammatory changes or ulceration are a contraindication for continuation of ablation therapy. Prior to any ablation therapy, a careful inspection of the residual Barrett's mucosa to detect suspicious areas is crucial. Here, special attention should be paid to nodular or sunken lesions. Suspicious areas should be biopsied, and in case of evidence of dysplasia, endoscopic resection should be performed.

Recommendation 4.15 (modified 2022)

After successful endoscopic resection and residual Barrett ablation, follow-up endoscopies should be performed at 3, 6, and 12 months, then annually.

[Recommendation, strong consensus]

Comment:

Recurrence of Barrett's mucosa and dysplasia occurs even after ER and complete ablation of Barrett's mucosa [463-465]. Since these recurrences are often amenable to renewed endoscopic therapy, control endoscopies should be performed at regular intervals even after complete ablation of Barrett's mucosa. The most frequent recurrences occur in the first year. For this reason, close monitoring is useful during this period. In a large study combining patients from the US and UK RFA registries, a complex statistical calculation demonstrated that the optimal monitoring intervals are 3, 6, and 12 months in the first year, and then annually [466]. Risk factors for recurrence were the initial length of Barrett's esophagus before therapy and the degree of dysplasia (LGD vs. adenocarcinoma).

Recommendation 4.16 (new 2022)

If submucosal infiltration is suspected, endoscopic submucosal dissection should be performed as an alternative to esophageal resection. If a low-risk situation is present (pT1 and sm1; <500 µm, L0, V0, G1/2, R0), endoscopic resection should be considered curative.

[Recommendation, strong consensus]

Comment:

The depth of infiltration of Barrett's carcinoma is crucial for the involvement of lymph nodes [467]. Lymph node metastases in patients with mucosal Barrett's carcinoma without the presence of risk criteria such as poor grade of differentiation (G3) and lymphatic vessel infiltration (L1) are a rarity, making endoscopic resection the treatment of choice. With infiltration of the submucosa, the rate of lymph node metastases increases significantly. The risk increases with increasing depth of infiltration. The submucosa is divided into thirds (T1sm1-3) to assess depth of infiltration. Additionally, tumor infiltration depth is measured in micrometers. In the presence of adenocarcinoma with superficial submucosal infiltration Tsm1; <500 µm and no other risk factors (L0, V0, G1/2, <20 mm, no ulceration), the risk for lymphogenic metastasis is very low. Manner et al treated 66 patients with low-risk lesions (infiltration sm1, L0, V0, G1/2, no ulceration). Complete remission was achieved in 53 patients. After a median follow-up of 47+29.1

months, the estimated 5-year survival rate was 84% [440]. Only one patient experienced lymph node metastasis during the follow-up period, thus the risk of lymph node metastasis was less than 2%. Retrospective work by other groups has confirmed the low risk of lymph node metastasis in patients with superficial submucosal infiltration [468, 469]. Surveillance intervals should be quarterly with endosocopy and endosonography for the first 2 years, then semiannually. A CT thorax and upper abdomen should be performed as a baseline examination and at 6 and 12 months. The additional performance of a PET-CT may be considered.

Recommendation 4.17 (new 2022)

Recurrent dysplasias can be treated again endoscopically.

[Recommendation open, consensus]

Comment:

Recurrences of Barrett's mucosa after complete ablation occur in 8-10% per patient-year during follow-up [470-472]. This recurrent Barrett's mucosa is found mainly in the first years of follow-up. This should be ablated again with RFA or APC.

Recurrent dysplasias may also occur during follow-up and are detected mainly at the cardia. These should be treated by focal endoscopic resection (ER or ESD).

Risk factors for recurrence include the degree of initial dysplasia before therapy and the length of Barrett's esophagus (higher risk of recurrence with longer Barrett's segment). Furthermore, significantly fewer recurrences occur in patients treated in an experienced Barrett's center with more than 10 ablations per year than in clinics with 3 or fewer ablation treatments per year (HR, 0.19;95% CI, 0.05-0.68) [473].

Recommendation 4.18 (new 2022)

Cylinder epithelial metaplasia <10mm at the Z-line is not considered Barrett's esophagus. In the absence of mucosal abnormalities, surveillance should not be performed in adults.

[Strong recommendation, strong consensus]

Recommendation 4.19 (modified 2022)

Depending on the presence of intraepithelial dysplasia, the following monitoring intervals are recommended:

1. No intraepithelial dysplasia: control after 1 year; if confirmed, control EGD should be performed every 3-5 years depending on other risk factors (Barrett's length, male sex, smoking);
2. Mild dysplasia: if visible lesion ER, otherwise RFA; alternatively, surveillance may be performed semiannually for 1st year, then annually
3. High-grade dysplasia: endoscopic therapy recommended.

[Recommendation/recommendation open, strong consensus]

Comment:

Monitoring seems to be useful for all patients in whom surgical or endoscopic therapy is possible in case of tumor detection.

The risk of malignant progression of nondysplastic Barrett's esophagus has been shown to be low in most studies in recent years. Hvid-Jensen et al. [83] has estimated the incidence to be 0.12% and Desai et al. [413] estimated it at 0.33% and 0.19%, respectively, for short-segment Barrett's. More recent studies also show incidence in this range [474, 475].

Surveillance intervals are based solely on the presence of dysplasia. Risk factors for developing HGDN or Barrett's adenocarcinoma in an analysis of nearly 3000 patients from a US and European database were length of Barrett's esophagus, male sex, smoking, and presence of LGD [476]. The authors Developed a point score with which to calculate the risk of developing HGD or Barrett's adenocarcinoma. The risk of progression was 0.5% annually in the low-risk group, 4.6% in the intermediate-risk group, and 12.3% in the high-risk group. In another analysis of a large cohort with Barrett's esophagus, advanced age >70 years, male sex, Barrett's length >3cm, lack of PPI use, and history of thrush esophagitis were identified as risk factors for developing dysplasia and Barrett's adenocarcinoma. A meta-analysis of 20 studies involving nearly 75,000 patients also confirmed the previously mentioned risk factors of older age, length of Barrett's esophagus, male gender, smoking, and presence of LGD.

In summary, especially the length of Barrett's esophagus, male gender, older age, and smoking seem to be relevant risk factors for the development of HGD or Barrett's adenocarcinoma. This should be considered when scheduling control endoscopies. However, with increasing age, a risk-benefit assessment should be performed to determine whether endoscopic surveillance is still useful.

Although no controlled prospective study exists to date demonstrating regular endoscopic surveillance in barrett's esophagus [477-482], all international guidelines recommend endoscopic surveillance [429]. In a meta-analysis by Copidilly et al, regular endoscopic surveillance of patients with Barrett's esophagus was shown to result in diagnosis of Barrett's adenocarcinoma at an earlier stage and a reduction in all-cause mortality and Barrett's adenocarcinoma-related mortality. However, even according to the authors, the results should be interpreted with caution because of relevant bias in most of the included studies.

If LGD is present, either RFA or regular follow-up endoscopies can be performed.

If a patient is diagnosed with HGIN, the same procedure applies as for mucosal Barrett's adenocarcinoma. If HGD is localizable, ER should be performed. The presence of high-grade dysplasia is associated with the presence of nonvisible carcinoma in approximately 40% [483]. In addition, Weston demonstrated in 15 patients with unifocal high-grade dysplasia that progression (multifocal high-grade dysplasia/carcinoma) occurs in 53.3% over the course of 3 years [484]. If high-grade dysplasia occurs multifocally, the risk of carcinoma is additionally increased [485].

5 Guideline - Eosinophilic Esophagitis - Epidemiology, Diagnosis, Therapy

Definition 5.1 (new 2022)

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease of the esophagus characterized by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation. Other systemic and/ or local causes of esophageal eosinophilia should be excluded.

[Strong consensus]

Comment:

The first international guideline on EoE was published in 2007 [486]. In the updated version published in 2011, EoE was defined as a chronic, immune-mediated disease of the esophagus characterized by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation [487]. This definition has subsequently been adopted unchanged by American and European guidelines [488-490]. By definition, other systemic and local causes of esophageal eosinophilia must be considered (*Table 8*). The differential diagnosis required in the [486-489] PPI-responsive eosinophilia (PPI-REE), a differential diagnostic criterion required in previous guidelines, was [490, 491] because PPI-REE and EoE cannot be distinguished clinically, endoscopically, histologically, or genetically, and PPI-REE is now considered a subphenotype of EoE [491, 492].

Table 8: Possible differential diagnoses of esophageal eosinophilia

Possible differential diagnoses of esophageal eosinophilia
Gastroesopheal reflux disease
Eosinophilic gastritis/gastroenteritis/colitis with esophageal involvement
Achalasia or other primary esophageal motility disorders
Hypereosinophilic syndrome
Crohn's disease with esophageal involvement
Infections (fungal, viral, parasitic)
Drug hypersensitivity
Pill Esophagitis
Autoimmune diseases, vasculitides
Graft-versus-host disease
Skin diseases with esophageal involvement (pemphigus, lichen)
Pseudodiverticulosis

Statement 5.2 (new 2022)

EoE and GERD are distinct entities that can coexist independently or influence each other bidirectionally.

[Strong consensus]

Comment:

GERD and EoE are the most common diseases of the esophagus, which are not epidemiologically mutually exclusive and therefore may statistically coexist without affecting each other. However, there is also evidence for possible complex bidirectional interactions of both diseases [493]. For example, GERD may have a role in the pathogenesis of EoE via disruption of mucosal integrity to increased transepithelial allergen permeability with subsequent allergenic immune activation [494]. Furthermore, it has been shown that EoE patients are more likely than healthy controls to exhibit acid hypersensitivity, which may be a consequence of a disturbance in esophageal mucosal integrity [495]. On the other hand, EoE may be associated with a number of structural and functional disorders of the esophagus, which in turn may promote gastroesophageal reflux [496, 497].

Statement 5.3 (new 2022)

The incidence and prevalence of EoE has increased and varies regionally. The incidence is a mean of 7.7 in adults and 6.6 in children per 100,000 population. The prevalence is a mean of 34.4 per 100,000 population.

[Strong consensus]

Comment:

Since the initial description in the early 1990s [498, 499] EoE has evolved from a casuistically described rarity to one of the most common inflammatory diseases of the esophagus. Epidemiological studies from Europe and North America have shown that the incidence and prevalence of EoE has increased significantly over the past 2 decades [500]. There are no epidemiological data from Germany. However, registry-based studies from neighboring Switzerland, Denmark, and the Netherlands have shown that incidences of EoE have increased approximately 20-fold since the mid-1990s, although endoscopy and esophageal biopsy rates have increased only modestly during this time period [501-503]. A recent meta-analysis, based on a total of 29 epidemiologic studies, described pooled incidence rates of 7.7 and 6.6 per 100,000 person-years for adults and children, respectively [504]. The pooled prevalence was 34.4 per 100,000 population and was higher for adults than for children (42.2 versus 34). Over time, published prevalence rates increased significantly by approximately 4-fold (from 15.4 to 63.2, p=0.011).

In population-based studies or nonselected endoscopy cohorts, the incidence of EoE ranged from 4.8% to 7.3% [505-507]. In patients who underwent endoscopy primarily for dysphagia, prevalence rates ranged from 10% to 25% [500, 508]. Predictive factors described were asthma, male sex, and typical endoscopic changes [508]. Regarding the prevalence of EoE in patients with bolus obstruction, a meta-analysis of 14 studies found that EoE was confirmed as the cause of bolus obstruction in half of the cases (54%) in which esophageal biopsies were obtained [509]. In recent studies from the United States, Australia, and Scandinavia with a total of more than 700 patients, EoE was causative for acute bolus obstruction in 16% to 33% of cases [510-513]. In a retrospective analysis from a pediatric tertiary center in the United States, EoE was identified as the cause of acute bolus obstruction in 26 of 35 children (74%) [514].

EoE can manifest at any age and is most commonly diagnosed in the third and fourth decades of life [33, 515]. In children, the age of manifestation is biparental. A first peak of manifestation is found in the first

three years of life, and the second is in adolescence. The male sex has a two- to threefold risk of developing EoE [500].

5.1 Possible risk factors

Individuals with pre-existing atopic conditions are at increased risk of developing an EoE [516]. The prevalence of concomitant atopic diseases, e.g. allergic rhinitis, asthma, atopic dermatitis) is more common in EoE patients than in the normal population, ranging from 28-86% in adults and 42-96% in children [517]. It is postulated that EoE is induced mainly by food allergens but also aeroallergens and is mediated by Th_2 helper cells [518]. Moreover, it has been shown that EoE, atopic dermatitis, and allergic bronchial asthma share a similar pattern of disease-specific transcripts, highlighting the common molecular etiology [519]. *De novo* emergences of EoE after oral immunotherapy (OIT) in children and adults with atopic diathesis have been described [520, 521]. In a systematic literature review published in 2014, 15 publications were reviewed and a prevalence of *de novo* EoE after OIT was reported to be 2.7 [522]. Therefore, current guidelines from the Canadian Society of Allergy and Clinical Immunology (CSACI) listed EoE as a relative contraindication for oral immunotherapy [523].

In EoE, a familial cluster and a genetic predisposition have been described [524, 525]. 1st-degree male relatives have up to 64-fold increased risk of developing EoE [524]. Monozygotic and dizygotic twins were affected by EoE in 41% and 22% of cases, respectively. In addition, genetic polymorphisms for EoE have been identified that show overlap with associated gene loci of other atopic diseases, e.g., TSLP (thymic stromal lymphopoietin), CCL26 (eotaxin-3) filaggrin (FLG), desmoglein (DSG1), and CAPN14 [519, 526].

Statement 5.4 (new 2022)

Untreated EoE is usually associated with chronic persistent inflammation, which can lead to esophageal remodeling with strictures and dysfunction.

[Strong consensus]

Comment:

A first prospective study of the natural history of EoE in 30 patients with follow-up of up to 11.5 years (mean 7.2 years) without steroid treatment showed an increase in dysphagia in 23% and improvement in 37% of cases [527]. However, dilatations were performed in 11 patients, which may have positively influenced the symptom course. Histologically, there was a decrease in the density of eosinophilic infiltration during the course, but an increase in fibrosis in 6 of 7 cases studied. In a retrospective study of 200 patients in the Swiss EoE cohort, it was shown that with increasing latency of diagnosis, the rate of esophageal strictures on index endoscopy increased [528]. If the diagnosis was made within 2 years of symptom onset, esophageal stenoses were found in 47% of cases. If the diagnosis was made after more than 20 years since symptom onset, the stricture rate increased to 88%. In the largest cohort study to date of 721 patients (including 117 children) from the Netherlands, the rate of endoscopic fibrosis signs at diagnosis was shown to be significantly higher in adults (76%) than children (39%) [529]. If the time to diagnosis was a maximum of 2 years, the rate of fibrosis signs at index endoscopy was 54%. The rates of high-grade strictures and bolus obstruction were 19% and 24%, respectively. With a

diagnostic delay of 21 years or longer, these rates increased to 52% and 57%, respectively. Based on these data, a risk of progression of 9% per year was calculated for untreated disease [529].

Comparable studies from the USA came to similar results [530, 531].

A manometric study also found a significant increase in esophageal motility disorders as a function of disease duration (0-5 years: 36%; ≥16 years 83%) [496].

The chronic relapsing nature of EoE is also supported by the courses of placebo-treated patients in prospective therapy studies. In a first remission maintenance study from Switzerland, placebo-treated patients relapsed after one year in 71% of cases [532]. A prospective observational study from the United States showed that within one year of initial steroid treatment, symptomatic recurrence occurred in 57%, which was also associated with histologic recurrence in 78% of these cases [533]. In a large European multicenter study, within one year of placebo treatment, clinical recurrence occurred in 60% of cases, endoscopic progression occurred in 60% of cases, and histologic recurrence occurred in over 90% of cases [534].

In pediatrics, studies of the long-term course of EoE are complicated by the fact that symptoms in childhood are often nonspecific and the clinical picture does not evolve toward dominant dysphagia until adolescence. In this respect, the appearance of new dysphagic symptoms over 6 years in 24 untreated children is not necessarily indicative of disease progression [535]. However, other findings indicate a similar natural history. Eosinophilic infiltration remained unchanged or even increased over the period [535] or even increased [536], with increasing eosinophilic infiltration of the esophageal mucosa being a marker for the increase or first occurrence of dysphagia. On the other hand, there are also favorable reports of regression of symptoms after therapy during the transition to adulthood [537].

Statement 5.5 (new 2022)

The most common symptoms in adolescents and adults are dysphagia and bolus obstruction. In infants and children, reflux symptoms, vomiting, abdominal pain, food refusal, and growth failure are most common.

[Strong consensus]

Comment:

The clinical presentation of EoE is very different in children and adults [538]. Adolescents and adults are dominated by dysphagia (70-80%) and bolus impaction (33-54%) [539, 540], but retrosternal burning is also a common accompanying symptom. In infants and young children, nonspecific symptoms such as reflux-like symptoms with vomiting (27%), nausea (27%), refusal to feed (14%), or failure to thrive are often found. Dysphagia (28%) and bolus obstruction (7%) also occur [539-541]. In clinical evaluation, especially in adolescents and adults, it is important to note that it is not uncommon for patients to develop adaptive strategies during the course of the disease and change their eating behavior to avoid symptoms, which can also lead to diagnostic delay [542]. For example, it has been shown that patients with active EoE chew significantly more often, consume significantly more fluids, and require significantly more time for complete consumption when eating a standard meal compared to healthy controls [543]. Therefore,

targeted questions regarding eating behaviors or avoidance strategies should also be asked during clinical evaluation to better capture clinical disease activity [542].

Another recently described symptom complex is the immediate food-induced response of the esophagus (Food-induced immediate response of the esophagus (FIRE)). It describes an unpleasant or painful sensation, independent of dysphagia, that occurs immediately after contact of specific foods with the esophageal mucosa. In a large survey of 57 EoE experts and 368 EoE patients, 90% of the experts and 40% of the patients reported having observed the FIRE symptom complex [544]. The most common triggers for FIRE symptoms were fresh fruits, vegetables, and wine. Endoscopic bolus removals were more common in male patients with FIRE symptoms.

Statement 5.6 (new 2022)

Health-related quality of life is relevantly reduced in children and adults with active EoE.

[Strong consensus]

Comment:

The chronic course, the limited therapeutic options and the need for close clinical and endoscopic-histological follow-up negatively affect the health-related quality of life (HRQOL, health-related quality of life) in children and adults. [545, 546]. This has psychological and social consequences [545]. Very significantly, bolus and choking anxiety as well as the general burden of the disease determine the HRQOL in adult and pediatric EoE patients [545, 547, 548]. As might be expected, symptom severity correlates strongly with HRQOL [545, 547-549]. Although available treatment options (e.g., topical corticosteroids) significantly improve HRQOL, on the other hand, overly restrictive diets such as the 6FED or elemental diets again have a negative impact on HRQoL [545, 547-549]. In addition, the EoE is associated with anxiety and depression [545, 547-549]. A retrospective study in children shows that 2/3 of the studied collective develop psychosocial stress, including social problems (64%), anxiety (41%), sleep disturbances (33%), depression (28%), and school problems in 26% of cases [547]. In adults, repeated bolus obstruction, dietary interventions, and persistence of symptoms associated with EoE represent the most important factors influencing the reduction of HRQOL [549]. This may lead to entrenched restrictive food intake and food-related anxiety. A recent study retrospectively assessed the prevalence of psychiatric comorbidities in a cohort of adult EoE patients [550]. There were 31% of patients with at least one psychiatric treatment indication or neuropsychiatric comorbidity, and 12% of the collective had a diagnosis of depression, followed by anxiety (9.3%). In another study, the Hospital Anxiety and Depression Scale 8 (HADS-8), a self-assessment questionnaire of depressive and anxiety symptoms, was applied to a cohort of Spanish EoE patients. Results showed that 31.1% and 9.8% suffered from anxiety and depression, respectively [551]. Studies on anxiety in children and adolescents show that, in particular, adolescents aged 11-17 LY with EoE are more likely to present with anxiety symptoms and depression compared to the healthy population [552].

Statement 5.7 (new 2022)

The most common endoscopic findings of EoE are whitish exudates, longitudinal furrows, mucosal edema, fixed rings, a small-caliber esophagus, and strictures. These may occur alone or in combination.

[Strong consensus]

Comment:

EoE is usually accompanied by endoscopically visible structural changes of the esophagus. While whitish exudates (corresponding to eosinophilic microabscesses), longitudinal furrows, and mucosal edema are signs of acute inflammation, fixed ring formation (so-called trachealization of the esophagus), a small-caliber esophagus, and strictures reflect a chronic fibrosis stage [530, 553]. Often, a strong vulnerability of the esophageal mucosa ("crepes-paper-sign") as well as a hard resistance during biopsy removal ("tug sign") can also be observed during endoscope massage [554, 555]. In adults, longitudinal furrows (80%), rings (64%), small-caliber esophagus (28%), whitish exudates (16%), and strictures (12%) are most common [556] while a retrospective study of 381 children most frequently described the presence of longitudinal furrows (41%), a normal finding (32%), whitish exudates (15%), and rings (12%) [557]. The endoscopic findings may be present alone, but more often occur in combination. Although they may not necessarily be present in every EoE patient, they can be detected in 90% of EoE patients. The better the endoscopist is trained for EoE, the higher the detection rate of abnormal findings [558]. However, a meta-analysis from 2012, which included 4678 EoE patients, could only show an insufficient association between endoscopic findings and disease activity [558]. Therefore, a biopsy for histological evaluation remains mandatory for diagnosis as well as for follow-up (e.g. therapy monitoring) [491].

Recommendation 5.8 (new 2022)

For endoscopic reporting of EoE, the EREFS classification should be used.

[Recommendation, strong consensus]

Comment:

The EREFS classification (acronym for exudates, rings, edema, furrows, and strictures) was published by Hirano et al. 2013 [559]. In a prospective multicenter study in adult EoE patients, this classification was shown to have good intraobserver and interobserver agreement among expert and inexperienced examiners. In other independent studies, the validity of the EREFS classification in children and adults was confirmed [560-563].

However, conflicting data have been described regarding the correlation of EREFS classification with histologic and clinical EoE activity. The prospective unicenter study by Dellon et al. was able to demonstrate a positive correlation [560], whereas von Rhijn et al. found no association between endoscopic and histologic activity [563]. A 2017 Spanish prospective multicenter study also showed no correlation between EREFS and histology, and EREFS and symptoms [564].

However, numerous studies have now demonstrated a parallel improvement in endoscopic activity based on EREFS classification as well as histologic activity after topical steroid therapy [565-571]dietary therapy [572, 573] and antibody therapy [574, 575] both in children [569-571] as well as in adults [534, 565-568, 572-575]

show. A simplified EREFS classification with comparable good accuracy was recently proposed by Schoepfer et al. [576].

Table 9: Modified EREFS score [Strong consensus]

Major findings	
Degree	**Rings**
0	None
1	Low (discreetly detectable)
2	Moderate (clear rings, passage with standard gastroscope possible)
3	Heavy (clear rings, passage with standard gastroscope not possible)
	Exudate
0	None
1	Mild (</= 10% of esophageal surface area).
2	Severe (> 10 % of esophageal surface)
	Furrows
0	None
1	Available
	Edema
0	None (mucosal vessels visible)
1	Present (mucosal vessels not visible or diminished).
	Stricture
0	None
1	Available
Minor findings	
	Crepe paper sign (mucosal laceration during endoscope massage).
0	None
1	Available

Recommendation 5.9 (new 2022)

At least 6 biopsies should be obtained from several levels of the esophagus, especially from regions with endoscopic abnormalities.

[Recommendation, strong consensus]

Comment:

For the diagnosis and monitoring of EoE, the taking of step biopsies of the esophagus is mandatory. These must be performed in any case, because even an inconspicuous endoscopy finding does not exclude EoE (in about 10% of adults and 32% of children). [557, 558]. In EoE, the eosinophilic inflammation of the esophagus shows an irregularly distributed pattern; it is a so-called "patchy disease" [577-581]. Therefore, diagnostic sensitivity is increased by taking multiple biopsies from at least two or more sections of the esophagus [582-584]. Furthermore, the biopsies should be taken from endoscopically

conspicuous areas if possible, because the highest inflammatory activity is to be expected here. In particular, macroscopically visible "white plaques", which correspond to microscopic eosinophilic microabscesses [585] and longitudinal furrows [586] show a high density of eosinophilic granulocytes. Biopsies from the stomach and duodenum should also always be obtained at initial diagnosis, even if the absence of symptoms or endoscopic abnormalities makes the presence of eosinophilic gastroenteritis unlikely [587, 588]. According to a recent retrospective study of 93 EoE patients with typical clinical presentation, the diagnostic gain with regard to relevant eosinophilic involvement of the stomach or duodenum was 3.6% [589].

Statement 5.10 (new 2022)

An eosinophil count of > 15 per high-resolution field of view (standard size 0.3 mm²) is considered a diagnostic threshold for EoE. The standard hematoxylin-eosin stain used in routine diagnostics is sufficient for histological evaluation of EoE.

[Strong consensus]

Comment:

The diagnostic threshold of >15 per visual field has been arbitrarily chosen in the past to differentiate EoE from other inflammatory esophageal diseases and especially from GERD [590-592]. Several studies have shown high accuracy for this threshold in diagnosing EoE [593, 594]. However, it should be noted that EoE and GERD are not mutually exclusive and may coexist in individual cases. Therefore, histologic findings are only one of several components in confirming the diagnosis of EoE. Since microscope fields of view may vary, it is recommended to report the eosinophil count per 0.3 mm^2 field of view to ensure standardization [490]. For assessment of eosinophil counts and other parameters, the hematoxylin-eosin stain (HE) is sufficient. Additional special stains or immunohistochemical stains are not required for diagnosis and are not helpful for differential diagnostic issues. In addition to eosinophil count, other characteristic features include eosinophilic abscesses, basal zone hyperplasia, dilated intercellular clefts, eosinophils in superficial epithelial layers, dyskeratotic epithelial cells, and fibrosis of the lamina propria [595]. A validated EoE-specific histology score (EoEHSS) was published in 2017 [596]. This provides semiquantitative grading and staging of these EoE-associated histologic features, enables standardized histologic reporting, demonstrates high interobserver agreement [596] and allows valid determination of disease activity [597]. The utility of using the EoEHHS in routine patient care outside of clinical trials, where it is currently in use [574, 575, 598], remains to be evaluated in the future.

Recommendation 5.11 (new 2022)

Noninvasive biomarkers for diagnosis or monitoring of EoE cannot be recommended at this time

[Recommendation open, strong consensus]

Comment:

Reliable non-invasive biomarkers would be highly desirable for diagnosis and especially for monitoring

of EoE in order to avoid repeated endoscopies with biopsy sampling. So far, however, a good correlation with esophageal eosinophilia and histological remission under therapy could only be shown for the absolute eosinophil count in blood [599-603]even though the diagnostic accuracy was only 0.754 and thus the overall sensitivity and specificity are insufficient [602]. Numerous other potential biomarkers in blood, stool, urine, breath and saliva (including eosinophil cationic protein [601-603], "eosinophil-derived neurotoxin" [599, 603, 604], mast cell tryptase [602], NO [605], eotaxin-3 and further chemokines [599, 602, 606] have so far proven to be insufficiently suitable for diagnosis and therapy monitoring [607]. Minimally invasive methods such as the "string" test or the "sponge" test, which are applied directly in the esophagus, have shown promising correlations between eosinophil-derived proteins and histological eosinophilia, but have not yet been further evaluated in large prospective studies [608, 609].

Recommendation 5.12 (new 2022)

Routine allergy testing should not be performed in adults.

[Recommendation, strong consensus]

Comment:

Already in the first studies on the 6-food elimination diet in adult EoE patients it could be shown that allergological diagnostics (skin prick test, serum IgEs) performed before starting the elimination diet are not able to reliably identify the allergen responsible for the EoE [610, 611]. Thus, in the study of Gonsalves et al. in 50 adult EoE patients the responsible allergen could be identified by skin prick test only in 13% of the cases [610]. In the study of Lucendo et al. in 77 patients sensitivities of 32% for food specific serum IgEs and 22.8% for the skin prick test were determined [611]. In another prospective study, an atopy patch test (APT) was performed in adult EoE patients before starting a 6-food elimination diet, and was positive in 50% of patients, but histologically confirmed in only 16% of cases [612]. The sensitivity of the APT to identify the responsible trigger was only 5.9%. In a prospective study from Australia, multiple allergological tests (skin prick test, skin patch test, allergen-specific serum IgE, basophil activation test, food-specific serum IgG) were tested in 82 adult EoE patients [613]. As a result, none of the tested tests was able to reliably predict the responsible allergen. The main reasons for the lack of reliability of allergological diagnostics are on the one hand test-specific limitations and on the other hand the fact that EoE is primarily regarded as a non-IgE-mediated disease [518]. For these reasons, a strong recommendation against allergological diagnostics, especially in adult EoE patients, was made in the European guidelines published in 2017 [490].

Recommendation 5.13 (new 2022)

Active EoE should be treated. Clinical symptoms, histology, and endoscopic findings should be considered to assess activity. The goal of induction and maintenance therapy is clinical and histological remission.

[Strong recommendation, strong consensus]

Comment:

Active EoE is associated with chronic, eosinophil-predominant esophageal inflammation, chronic recurrent esophageal symptoms, and significantly reduced quality of life [490]. If the disease is left untreated, there is a high risk for esophageal fibrosis, strictures, and bolus obstruction [528, 529, 541]. For these reasons, current European and U.S. guidelines recommend that if active EoE is detected, induction therapy should be initiated with the goal of achieving clinical histologic remission [490, 614]. This should be monitored clinically and endoscopically-histologically after 8 to 12 weeks. After achieving a clinical-histological remission, remission-maintaining therapy should be continued (*Figure 6*: Therapy algorithm modified according to [490, 615]).

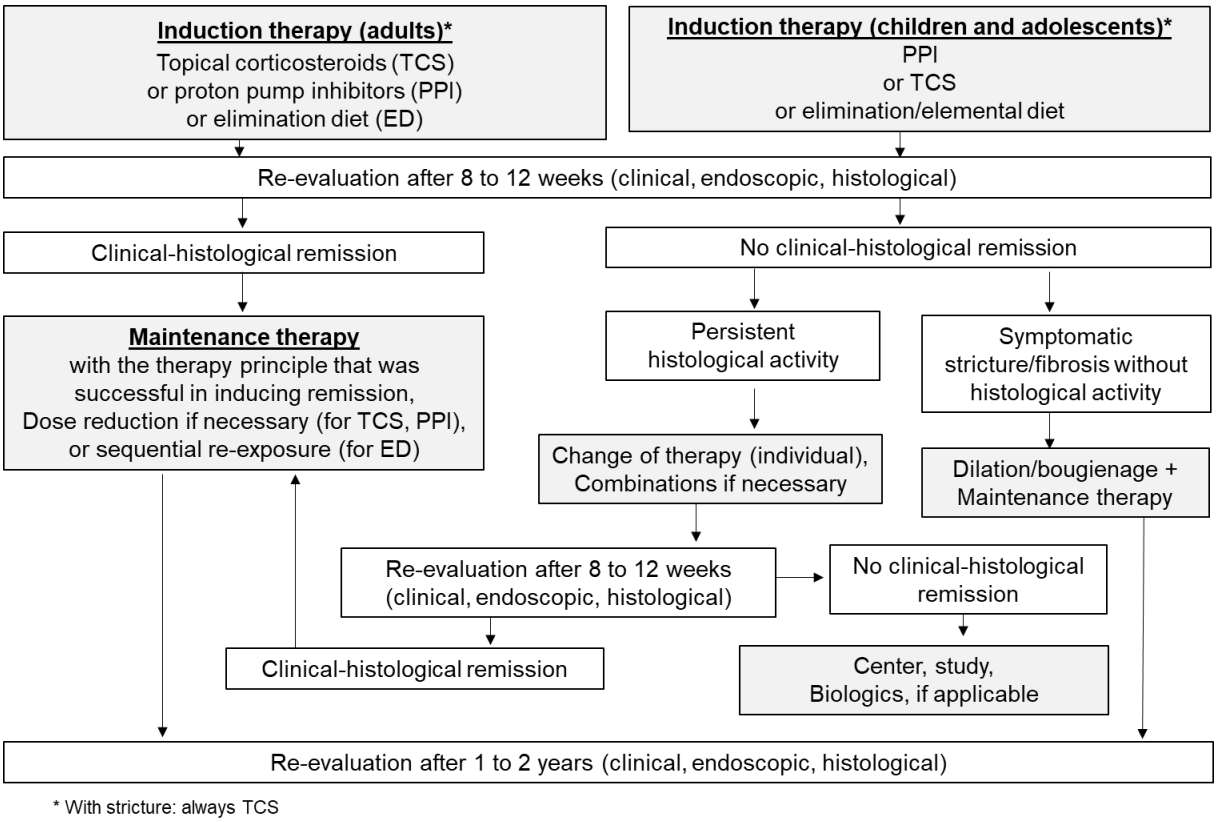


Figure 6: Therapeutic management of eosinophilic esophagitis - therapy algorithm modified according to [490, 615] (consensus)

Recommendation 5.14 (new 2022)

In adults with active EoE, therapy with topical corticosteroids should be given for remission induction (histologically and clinically). Alternatively, in adults with active EoE, therapy with high-dose proton pump inhibitors or a 6-food elimination diet may be used for remission induction (histologic and clinical).

[Recommendation/recommendation open, consensus]

Comment:

For remission-inducing therapy of EoE with topical corticosteroids in adults and children, 11 placebo-controlled double-blind studies are available to date, including 7 studies with budesonide and 4 with

fluticasone [567, 568, 598, 600, 616-622]. In addition, 5 randomized trials with other comparators exist: Fluticasone vs. prednisolone [623], fluticasone vs. esomeprazole [624, 625], budesonide suspension vs. budesonide nebulizer [626], budesonide suspension vs. fluticasone nebulizer [566]. In addition, 6 meta-analyses are available [627-632].

Previous studies have used swallowed asthma medications or individually prepared dosage forms at various doses and durations (budesonide: 1 to 4 mg per day, 2 to 12 weeks; fluticasone 880 to 1760 ug per day, 4 to 12 weeks) [600, 616-619]. In more recent studies, budesonide and fluticasone have been used in dosage forms specifically designed for the treatment of EoE [567, 568, 598, 620-622]. To date, only the orodispersible budesonide tablet has been approved in Germany for the treatment of active EoE in adults [633]. In the European registration study, the daily dose of 2 x 1 mg achieved clinical histological remission in 58% and 85% of cases after 6 and 12 weeks, respectively [567]. The rate of endoscopic remission was 61% at 6 weeks and 68% at 12 weeks. The differences from placebo in the primary endpoint and almost all secondary endpoints were highly significant. With excellent overall tolerability, only 5% of patients developed mild, symptomatic local candidiasis, which in no case led to discontinuation of local steroid therapy. Compared with placebo, there were no significant or clinically relevant changes in morning serum cortisol levels [567]. In an open-label multicenter induction study of 181 adults with active EoE, these results were confirmed [634]. In this cohort, 6 weeks of treatment with the orodispersible budesonide tablet (2 x 1 mg daily) resulted in clinical histologic remission in 70% of patients. The rate of histologic remission was 90.1%. In both studies, 6 weeks of treatment already led to a significant improvement in quality of life [567, 634, 635]. A network meta-analysis of all drug interventions tested to date (17 studies, 1011 patients) published in 2020 showed that orodispersible budesonide tablet 2 x 1 mg daily was the most effective therapy for remission induction of EoE [630]. Both the European guideline published in 2017 and the U.S. guideline published in 2020 recommended treatment with topical corticosteroids for remission induction of the [490, 614]. The more recent American guideline found a higher level of evidence for topical corticosteroids and formulated a stronger recommendation than for the other treatment options [614].

In a phase 3 pivotal trial published in 2021 and conducted in the United States, an esophageal-specific budesonide suspension at the daily dose of 2 x 2 mg was tested in 318 patients with active EoE aged 11 to 55 years [598]. After 12 weeks of treatment, the endpoints of histologic remission (</= 6 eosinophils/hpf) and clinical remission were achieved in 53.1% (placebo 1%) and 52.6% (placebo 39.1%), respectively. The EREFS score was also significantly improved. The rate of esophageal candidiasis was 4%. Passive adrenal insufficiency was observed in 2 patients (0.9%), manifested by fatigue in only one patient. Sixteen patients in the budesonide group (8.2%) and 3 patients in the placebo group (3.6%) showed reductions in maximum cortisol levels in the ACTH stimulation test at week 12, which were not considered clinically substantial [598].

A meta-analysis published in 2016 evaluated 33 studies of PPI therapy in a total of 619 patients with esophageal eosinophilia or suspected EoE, of which 21 were retrospective, 10 prospective, and 2 randomized [636]. In the overall results, the pooled histologic remission rate was 50.5% (< 15 Eos/hpf) and the clinical response rate was 60.8%. In subgroup analyses, remission rates tended to be higher with higher PPI dose and pathologic pH metrics, but the differences were not statistically significant. The

meta-analysis also indicated significant heterogeneity and publication bias. In a prospective observational study also published in 2016, a clinico-histological remission rate of 33% was reported in 121 adult patients with active EoE after 8-week, high-dose PPI therapy (omeprazole 2 x 40 mg daily) [637]. In a prospective registry study published in 2020, interim analysis of 630 patients (554 adults) after PPI therapy showed a histologic remission rate of 48.8% (<15 Eos/hpf) and 37.9% (<5 Eos/hpf), respectively [638]. Clinical response (reduction in dysphagia symptom score <50%) was documented in 71% of EoE patients. Higher histologic remission rates tended to be achieved with high-dose PPI therapy (double the standard dose) (50.7% vs. 36.7%). Combined clinical-histologic remission was also higher after high-dose PPI therapy (50.8%) compared with standard- or low-dose (35.8%). Longer duration of therapy was also associated with a higher clinicopathologic remission rate. In patients with a fibrostenotic phenotype, PPI therapy resulted in histologic remission in only 26.7% of cases and in 50.3% of cases in patients with an inflammatory phenotype.

Another recent retrospective study of 223 adult EoE patients from a US tertiary center reported a non-response of 71% after 8 weeks of high-dose PPI therapy [639]. Predictors of PPI nonresponse were young age, BMI ≤25.2 kg/m^2 , and peripheral eosinophilia >460per mm^3 . An endoscopically impassable stenosis/ stricture was associated with a high risk of PPI nonresponse (OR 9.06).

To date, only 2 randomized trials exist from 2010 and 2013 comparing 8 weeks of esomeprazole 40 mg daily therapy with aerolized fluticasone 2 x 440 µg daily in 25 and 42 patients, respectively [624, 625]. In the study by Peterson et al. [624] the histologic remission rate (</= 5 Eos/hpf) was 33% after esomeprazole (4/12) and 15% after fluticasone (2/13). In the study by Moawad et al. [625] similar histologic response rates (33% vs. 19%) were reported. To date, no placebo-controlled studies exist on the efficacy and safety of PPI therapy in EoE.

The 6-food elimination diet eliminates the foods most commonly associated with food allergies, i.e., cow's milk proteins, wheat, soy, egg, nuts, and fish/seafood. In a retrospective study in children, it was shown that up to 74% of the patients treated in this way showed histological remission, but when the individual foods were reintroduced by means of renewed endoscopies, the respective triggering food could be identified in only a few patients [640, 641]. In a prospective study of 50 adult EoE patients, histologic remission (<5 eos/hpf) was achieved in 64% of cases and improvement in symptom score in 95% after a 6-week, 6-food elimination diet [610]. After reintroduction of the food groups, histologic relapse occurred in all cases, matching the initial eosinophil count. In another prospective study of 77 EoE patients, the 6-food elimination diet resulted in histologic remission after 6 weeks in 73% of cases [611]. A meta-analysis published in 2014 found histologic remission rates of 73% in children and 71% in adults after 6-food elimination diet on the basis of 7 studies (4 of which were in children) [642]. The 6-food elimination diet places very high demands on the affected patients in everyday life. In order to ensure an effective therapy and the necessary compliance, the support of a nutritionist experienced in this form of therapy must be guaranteed. It is also important to recognize and correct possible malnutrition or nutritional deficiencies in good time. In 2017, a working group of the *American Academy of Allergy, Asthma and Immunology* published very comprehensive recommendations and algorithms for the therapy of EoE with elemental/elimination diets, which provide good orientation in this complex subject area [643].

Recommendation 5.15 (new 2022)

Systemic corticosteroids should not be used to treat EoE.

[Recommendation, strong consensus]

Comment:

Only one randomized trial exists comparing systemic prednisone and topical fluticasone in 80 children with EoE [623]. Prednisone was given at a dose of 2 x 1 mg/kg/day and fluticasone at a dose of 4 x 220 µg/day (age < 10 years) or 4x 440 µg/day (age 11-18 years) for a duration of 4 weeks, with subsequent tapering over 8 weeks. The primary endpoint of "histologic response" at 4 weeks (score of percent basal cell hyperplasia and eosinophil density) was achieved by 94% of patients in both groups. Symptom response (72% vs. 65%) and clinical recurrence rates were also comparable. Systemic adverse events were observed in 40% of cases under prednisolone and local candidiasis in 15% of cases under fluticasone. A potential benefit of systemic corticosteroids in EoE patients who do not respond to topical corticosteroids is not supported by studies.

Recommendation 5.16 (new 2022)

Initially, remission-maintaining therapy should follow the treatment principle that has been successfully used in induction therapy.

[Recommendation, strong consensus]

Comment:

After successful induction of remission of EoE, clinical and histologic recurrences are common [532-534]. Therefore, remission-maintaining therapy is necessary in the majority of cases. To date, 2 randomized, placebo-controlled trials of remission-maintaining therapy with topical budesonide exist [532, 534]. In a randomized, placebo-controlled, double-blind study of 28 patients published in 2011, remission-maintaining therapy with budesonide suspension 2 x 0.25 mg daily resulted in a significantly lower rate of histologic recurrence after 50 weeks. The rate of histologic remission at 50 weeks was 36% with budesonide and 0% with placebo. The rate of clinical remission at 50 weeks was also higher compared with placebo, but not statistically significant [532].

A European phase 3 study of 204 adult EoE patients in clinical histological remission demonstrated the efficacy and safety of orodispersible budesonide tablet in maintaining remission [534]. In this randomized double-blind study, the primary endpoint of clinico-histological remission was achieved after 48 weeks of therapy with orodispersible budesonide tablet at the daily dose of 2 x 0.5 mg or 2 x 1 mg in 73.5% and 75% of patients, respectively ($p<0.0001$ vs. placebo: 4.4%). The orosdispersible budesonide tablet was also significantly superior to placebo in other secondary endpoints (e.g., endoscopic remission, reduction in eosinophil count/hpf, time to clinical relapse, quality of life). In the placebo group, 90% of patients experienced histologic recurrence with an average high eosinophil count. In 60% of placebo patients, moderate to severe endoscopic manifestations of EoE recurred during follow-up. The rate of histologically confirmed symptomatic local candidiasis was 5.9% and 1.5% in budesonide-treated

patients and did not lead to treatment discontinuation in any case. Morning serum cortisol levels were not significantly affected.

Further evidence for the benefit of long-term therapy with topical corticosteroids is also shown by retrospective analyses of the Swiss EoE cohort [644, 645]. Thus, in 206 patients with a median follow-up of 5 years, therapy with topical corticosteroids was associated with a significantly lower risk of bolus obstruction (OR 0.41; 0.20-0.83). The effect was dependent on the duration of exposure [644]. Another analysis of 229 patients with a median follow-up of 5 years found that long-term therapy with topical corticosteroids was associated with significantly higher rates of clinical remission (31% vs. 4.5%), histologic remission (44.8%, vs. 10.1%), and endoscopic remission (48.8% vs. 17.8%) compared with no therapy [645]. Higher cumulative doses of topical corticosteroids and longer treatment duration were significantly associated with higher rates of clinical and complete remission. Another retrospective study of 82 patients who were continued on topical corticosteroids for remission maintenance after achieving histologic remission showed that patients on low steroid doses (<0.5 mg/d) tended to have more frequent (72% vs. 54%, n.s.) and significantly earlier (1.0 vs. 1.8 years, p=0.03) histologic recurrences compared to those on higher steroid doses (>0.5 mg/d) [646]. Both the European guideline published in 2017 and the U.S. guideline published in 2020 recommended remission-maintaining therapy with topical corticosteroids [490, 614].

No randomized controlled trials are available on long-term therapy of EoE with PPI. In a retrospective, multicenter cohort study of 75 adult patients who initially went into remission with high-dose PPI therapy, PPI maintenance therapy (20- 40 mg 1x daily) maintained remission in 73% of cases after one year [647]. In a prospective study of 121 adult therapy-naive EoE patients, remission was achieved in only 40 patients (33%) after 8 weeks of therapy with omeprazole 2 x 40 mg daily. After reduction of the PPI dose to 40 mg omeprazole daily, remission was maintained in 31 patients (31% of the initial population). With further dose reduction to 20 mg omeprazole daily, only 15 patients remained in remission [637].

An interim analysis of a registry-based cohort study examined the effectiveness of PPI therapy in 630 patients (554 adults) with EoE [638]. After PPI-induced clinical histologic remission, 172 patients (60% of the remission group) were maintained on a PPI. Maintenance therapy was recorded a median of 112 days after achieving remission. In 138 patients, the PPI dose was reduced, in 20 patients the PPI dose was increased due to symptoms, and in 14 patients the PPI was changed. Remission was maintained with the reduced PPI dose in 72/138 (69.2%). A "deep histologic remission" (<5 Eos/HPF) was evident in 62/138 patients. Clinical remission was exhibited by 84/138 patients. A combined clinical/histological remission was seen in 72/103. However, this analysis was based on only 90 complete patient records, 48 (34.7%) patient records were not evaluable or incomplete.

Few data are available on the long-term therapy of EoE in adults using an elimination diet. In a prospective single-center study, 49 of 67 patients (73%) achieved histologic remission after a 6-week, 6-food elimination diet [611]. A subsequent stepwise re-exposure protocol was fully completed by 42 patients. In approximately one-third of patients each, one, two, or three or more responsible food triggers were identified. After one year, 25 patients who continued elimination of the responsible food triggers were still in histologic and clinical remission. After two and three years, remission was documented in 15 and four patients, respectively. In a retrospective study, 21 of 52 patients who achieved histologic remission after initial elimination diet (6-food and/or allergy test-based) (40%) were followed up for a

mean of 25 months [572]. Only 10 patients remained in remission with continued elimination diet. In 8 of 11 cases, relapse was due to lack of compliance. Even the longer-term elimination diet should always be accompanied by an experienced nutritionist to ensure the necessary compliance and to be able to react to possible malnutrition or malnutrition in a timely manner [643].

Statement 5.17 (new 2022)

Symptoms do not reliably correlate with histologic activity of EoE.

[Strong consensus]

Comment:

Typical clinical symptoms in adults include esophageal dysphagia and the occurrence of bolus impaction, less commonly regurgitation, heartburn, and chest pain [539, 648]. In children, on the other hand, reflux symptoms, nausea/vomiting, abdominal pain, refusal to eat and failure to thrive are often the main symptoms [535]. Objective assessment of EoE symptoms is often difficult. Although validated questionnaires exist to quantify disease activity and its impact on quality of life, they often show an insufficient correlation with the histological activity of the disease [649, 650]. For adult EoE patients, Schoepfer et al. developed the Eosinophilic Esophagitis Activity Index (EEsAI-PRO), which measures the patient's difficulty in swallowing different food consistencies as well as dietary and behavioral modifications [651]. Other validated questionnaires include the " Dysphagia Symptom Questionaire (DSQ)" for adults [652] and the Pediatric EoE symptom Score V 2.0 (PEES) for children [653]. The impact on quality of life can be assessed using the EoO-QoL-A for adults and the [654] and by means of the PedsQL for children [655] for children. The discordance between inflammatory activity and patient-perceived symptoms may be due to the presence of therapy-refractory stenoses [528]. In addition, a reduced distensibility of the esophagus can be observed in many adult and pediatric EoE patients, which can be determined by means of a special measuring catheter (endoluminal functional lumen imaging probe (EndoFLIP) during an endoscopy [656, 657]. It could be shown that the distensibility of the esophagus also does not correlate with the histological inflammatory activity. On the other hand, reduced distensibility may be a predictor for the occurrence of bolus impaction [658].

Recommendation 5.18 (new 2022)

The effectiveness of induction therapy should be assessed clinically and endoscopically-histologically after 8 to 12 weeks.

[Strong recommendation, strong consensus] *(Decide Wisely).*

Comment:

The goal of successful induction therapy is both clinical-histological remission and improvement of endoscopic findings. Validated questionnaires (e.g. ESAI-PRO, DRQ for adults, PEES2 for children) or a numerical scale are suitable for the objective assessment of symptoms [651-653]. Endoscopic findings should be recorded in a standardized way using the EREFS classification [559]. At present, only endoscopy

with biopsy is suitable for checking the presence of histological remission, because symptoms and endoscopic findings often correlate poorly with inflammatory activity [562, 649]. So far, there are no reliable non-invasive biomarkers either [602, 606]. Review of induction therapy is usually recommended after 8-12 weeks [487, 490, 659]although no study has yet evaluated the best time to review induction therapy. Alexander et al. demonstrated in a prospective study in which 42 adult patients were treated with topical fluticasone or placebo that performing an endoscopy later than 3 months showed no additional information in case of failure of induction therapy [618].

Recommendation 5.19 (new 2022)

The effectiveness of remission-maintaining therapy should be assessed clinically and endoscopically-histologically every 1-2 years.

[Recommendation, strong consensus]

Comment:

Due to the chronic progressive nature of the disease, EoE patients should receive permanent remission-maintaining therapy after successful induction therapy [500]. In principle, this can take the form of continuation of drug therapy, if possible at a reduced dose, or long-term elimination of identified food allergens (-> Fig. Algorithm). So far, only few data exist on the optimal verification of remission-maintaining therapy. The prospective randomized studies published so far (exclusively with STCs) chose a therapy duration of 12 months before renewed clinical and endoscopic-histological evaluation [532, 534, 660]. In retrospective observational studies with STCs or PPI [569, 637, 644, 645, 647, 661, 662] which cover an average duration of therapy of up to 6 years, or prospective studies with elimination diets, a 12-month duration before re-evaluation was also chosen by the majority [611]. The majority of retrospective studies with STCs or PPIs or prospective studies with elimination diets have also chosen a 12-month interval of clinical, endoscopic, and histologic review. For this reason, the European guideline on the clinical management of EoE also recommends corresponding follow-up intervals of 1 to 2 years [490].

Recommendation 5.20 (new 2022)

Empiric 4-food or 2-food elimination diets can be considered, but these are less effective than the 6-food elimination diet.

[Recommendation open, strong consensus]

Comment:

In 2018, Molina-Infante demonstrated in a study of adult and pediatric patients that elimination of common allergens, such as the combination of milk and gluten, resulted in clinical and histologic remission in approximately 43% of patients studied [573]. In 2017, Kalgawalla showed remission of approximately 64% in children who received 4-food elimination (milk, egg, wheat, soy) [663]. In adults, remission rates of 54% were described [642]. In addition, there are individual pediatric studies that have shown that elimination of individual foods, such as cow's milk proteins, can also lead to significant

improvement [664, 665]. In a prospective study of 41 children and adolescents, it was shown that 1-FED consisting of the elimination of cow's milk protein as the most common allergenic trigger of EoE can induce histological remission in 51%, endoscopic improvement in 59%, and improvement of previously reported symptoms in 61% of cases [665]. Thus, these diets are alternatives, but they are significantly inferior to 6-food elimination. Particularly in pediatrics, single-food elimination is an alternative for patients or patient parents, despite its lower effectiveness, because it may have greater adherence than a more complex elimination diet or drug therapy [666].

Recommendation 5.21 (new 2022)

Allergy test-based elimination diets should not be used in adults due to limited efficacy.

[Recommendation, strong consensus]

Comment:

In a meta-analysis published in 2014, a total of 14 studies of allergy test-guided elimination diet with a total of 626 EoE patients were identified after systematic literature search Kagalwalla [642]. Of these, only 2 studies included adult EoE patients (n=32) [667, 668]. While the overall effectiveness of the allergy test-guided elimination diet was reported to be 45.5%, it was only 26.6% and 35%, respectively, in adults. Due to the low success rate of the allergy test-guided elimination diet, this treatment modality is explicitly not recommended in the 2017 European guideline for adult EoE patients [490].

Statement 5.22 (new 2022)

The elemental diet shows high effectiveness. However, due to the frequent adherence problems, especially in adolescence, its practical usefulness in the treatment of EoE is very limited.

[Consensus]

Comment:

The elemental diet is an amino acid-based formula diet that is superior to all other dietary therapies in terms of histologic remission [669-672]. A meta-analysis showed a remission rate of 90.8% [642]. However, practical feasibility is difficult for various reasons (unpleasant taste, probe application may be required). In a large study, a nasogastric tube had to be placed in 80% of the children. This results in additional treatment costs, and in very young children it may even have a negative influence on the development of the facial muscles and taste formation due to the exclusive feeding of liquid food [672].

Recommendation 5.23 (new 2022)

Endoscopic dilatation/bougienage should be performed for refractory, symptomatic esophageal strictures.

[Strong recommendation, strong consensus]

Comment:

Esophageal strictures are often responsible for dysphagia in EoE and are the main risk factor for bolus impaction [528, 673]. Endoscopic dilatation, which can be performed using either "through the scope" balloons or wire-guided Savary bougies, is therefore a valuable therapeutic option. However, it does not influence the underlying eosinophilic inflammation [674]. Endoscopic dilatation should therefore be performed only in cases of residual strictures despite drug response. In a metanalysis of 525 adult EoE patients and a total of 992 dilations, clinical improvement was shown in 75% of patients [675]. The incidence of perforation was described as 0.3%. In two other meta-analyses with 671 and 977 patients, the perforation rate was reported as 0.1% and 0.03%, respectively [676, 677]. The occurrence of postinterventional hemorrhage was also a very rare complication, 0.1% and 0.03%, respectively [675, 677]. In addition, there were no differences in complication rates with respect to the different dilatation techniques [677]. The occurrence of an intended mucosal tear is not a complication of endoscopic dilatation treatment. However, due to the often very rigid esophageal wall, a maximum dilatation of 3 mm should be performed per dilatation treatment [678]. Symptomatic improvement can be assumed when an esophageal lumen of 16-18 mm has been achieved [678].

Recommendation 5.24 (new 2022)

Immunomodulators (azathioprine, 6-mercaptopurine) or antiallergic drugs (montelukast, cromoglycic acid, chemoattractant receptor homologous molecule for TH_2 - cells ($CRTH_2$)-antagonist) should not be used in the therapy of EoE.

[Strong recommendation, strong consensus]

Comment:

Azathioprine or 6-mercaptopurine has been studied only in a small case series in steroid-dependent course of EoE [679]. In this study, three patients with EoE (one patient with eosinophilic gastroenteritis and esophageal involvement) were treated with azathioprine (2.0- 2.5 mg/kg bw daily p.o.) . One patient was switched to 6-MP during the course because of nausea. Steroids could be spared and phased out under immunosuppressive therapy. All three patients showed a long-lasting steroid-free remission after initiation of therapy with azathioprine/6-mercaptopurine.

Although mast cells play a pathogenetic role in EoE [680] 4 weeks of therapy with cromoglycic acid (mast cell inhibitor) has shown neither clinical nor histologic response in 14 children with EoE [557]. Montelukast (leukotriene D4 receptor antagonist) was studied in 8 adult patients with EoE at sometimes high doses (10-100 mg daily) over a median period of 14 months [681]. Symptomatic improvement was observed in 8 /12 patients, but histologic remission was not achieved even after 4 months of therapy. A case series in 8 children with EoE treated with montelukast (4-10 mg daily) recorded symptomatic response in 3/8, but histologic response was absent [682]. A standard dose of montelukast (10 mg daily) failed to maintain steroid-induced remission in EoE in a case series of 11 adults. After 3 months on anti-allergic therapy, clinical/histological recurrence occurred in all cases [683].

Chemoattractant receptor-homologous molecule for TH_2 cells ($CRTH_2$)antagonist was evaluated in a randomized, double-blind, placebo-controlled trial in 26 adult EoE patients (steroid-dependent or

steroid-refractory) [684]. Compared with the placebo group, significant clinical and histologic improvement was seen with 100 mg after 8 weeks, but histologic remission was not achieved.

Recommendation 5.25 (new 2022)

Biologics are currently intended to be used in the treatment of EoE only in clinical trials.

[Strong recommendation, strong consensus]

Comment:

To date, there are 2 biologics (dupilumab, RPC4046) that have demonstrated efficacy in the treatment of EoE in phase 2 trials. Dupilumab is a human recombinant IgG4 monoclonal antibody whose pharmacologic effects are based on binding to the alpha subunit of the interleukin (IL) -4 receptor and the IL-13 receptor. IL- 4 represents a key cytokine in Th_2 -mediated diseases and is highly overexpressed in esophageal mucosa in EoE patients and measurable elevated in serum [685]. IL- 13 is secreted by Th_2 cells and is also a key cytokine in the pathogenesis of EoE [686, 687]. In a randomized, placebo-controlled phase 2 trial in 47 -adults with active EoE, 12 weeks of therapy with dupilumab 300 mg subcutaneously showed significant clinical, histologic, and endoscopic improvements at 10 weeks [575]. The Straumann Dysphagia Index (primary endpoint) decreased by a mean of 3 points (p=0.0304). At week 12, a significant decrease in maximum intraepithelial eosinophil count was seen (mean reduction of 86.8 Eos/HPF, reduction 107.1%; p< 0.0001 versus placebo). Histologic grading and staging (EoE-HSS) and esophageal distensibility improved significantly (p< 0.0001). Dupilumab is currently being evaluated in a phase 3 trial in adults with active EoE [688].

The recombinant humanized anti-IL-13 antibody RPC4046 was tested in a randomized, placebo-controlled phase 2 study in 100 adult patients with EoE at 2 doses (180 mg, 360 mg) subcutaneously 1x weekly for 16 weeks [574]. The primary endpoint (significant reduction in mean eosinophil count) was met in both verum groups. In the 360 mg group, the endoscopy score (EREFS) also improved significantly. Dysphagia score also improved in this group, but not statistically significantly. 86 patients were subsequently enrolled in an open-label extension study and continued on RPC 360 mg/week s.c. for 52 weeks [689]. After 12 weeks, the mean esophageal eosinophil count in patients in the former placebo group had dropped to values in the two verum groups and was maintained until week 52. The ERFEFS score at week 12 also improved in this group. The former verum groups showed further numerical improvements at weeks 12 and 52. The most common adverse events (AEs) were upper respiratory tract infections (21%) and nasopharyngitis (14%).

Other biologics approved for severe bronchial asthma (mepolizumab (anti-IL-5), reslizumab (anti-IL-5), omalizumab (anti-IgE), among others) have been studied in randomized, double-blind, placebo-controlled trials in children, adolescents, and adults with EoE [690-693] have been investigated. None of these studies achieved clinical histologic remission. The anti-IL13 antibody QAX576 also failed to show a clinical response in a randomized, double-blind, placebo-controlled study in adults with EoE [694]. The anti-TNFα antibody infliximab was administered intravenously at standard doses at weeks 0 and 2 in a case series of three adult patients with EoE. Neither symptomatic nor histological response was achieved after week 6 [695].

5.2 Special features in pediatrics

Recommendation 5.26 (new 2022)

In children and adolescents, a nutritionist experienced in food allergies should be involved from the time of initial diagnosis, since failure to thrive must be prevented or, if necessary, corrected.

[Recommendation, strong consensus]

Comment:

Food elimination is an effective therapeutic principle in children and adolescents with EoE that can lead to long-term remission without the use of medications not yet approved for childhood and adolescence [642, 696]. However, the initiation and monitoring of elimination diets is a major challenge for the care team and for the family, especially since there are no adequate tests for the safe identification of EoE-triggering foods. Groetch et al. have summarized the findings of an American Academy of Allergy, Asthma and Immunology working group on the management of dietary modifications in EoE in a very detailed review paper, with practical tips for individualized counseling [643]. To avoid malnutrition or even eating disorders, guidance of the family by an experienced nutritionist is strongly recommended. The work of Groetch et al. [643] provides a good basis for this.

Recommendation 5.27 (new 2022)

In active EoE without stricture in childhood and adolescence, oral high-dose PPI therapy should be the primary treatment for remission induction (clinically and histologically).

[Recommendation, strong consensus]

Comment:

Treatment with PPI in childhood and adolescence is an effective, inexpensive, readily available and applicable therapeutic option with few side effects. Available data show that therapy with PPI results in both clinical response and histologic remission in a large proportion of patients with characteristic clinical, endoscopic, and histologic findings of EoE and normal long-term impedance pH-metry testing [636, 697].

In a prospective study, 8 weeks of high-dose PPI treatment (2x1 mg/kg bw/d esomeprazole) in 51 children with symptoms of esophageal dysfunction and esophagomucosal eosinophilia resulted in histological remission (<15 Eos / HPF) achieved in 68.6% and complete disappearance of eosinophilic infiltration (<5 Eos / HPF) in 47% [662].

Recently published data from a study with cross-sectional design of the EUREOS EoE CONNECT registry (76 children and 554 adults) confirm previous studies for childhood. In a collective of 76 children studied, approximately 42% achieved histologic remission with PPI therapy. Half of the initially successfully treated children and adolescents remained in remission after dose reduction [638]. All PPI agents used were comparably effective, and administration for 10-12 weeks achieved the highest benefit for achieving remission [638]. The authors further demonstrated that PPIs did not show sufficient therapeutic efficacy in cases of already stenosing EoE . In these cases, topical steroid therapy should

be used first [638] (see also statement 29). It was also shown at the molecular level that it reduces the expression of relevant genes (including eotaxin-3) in the esophageal epithelium, thereby normalizing the inflammatory transcriptome in children with EoE [697, 698]. In vitro studies support that PPIs may have an anti-inflammatory effect that is independent of the ability to block acid [698-700].

Two molecular genetic studies found preliminary evidence (implementation of GWAS, Shoda et al. 2017 [701]) for a number of identified candidate genes that may predict PPI sensitivity in EoE patients (including a gene encoding the potassium channel (KCNJ2 / Kir 2.1) [701, 702].

Furthermore, Canas et al. succeeded in identifying a specific mucosal mRNA expression pattern at diagnosis in 43 children with EoE and thus a potential biomarker for PPI responsiveness [703]. If these results can be reproduced in further studies, this would represent an important step towards individualized and tailored therapy decisions.

Thus, in summary, these studies provide evidence at the pathophysiologic level for the value of PPI agents in the treatment of EoE.

Despite the obvious inferiority in terms of efficacy (achievement of histological remission in approximately 48-69% of cases with PPI [697, 703] and >90% of cases with budesonide treatment [571], randomized, controlled, prospective head-to-head studies are lacking), the substance group of PPIs should be used as the preferred initial treatment due to the positive treatment data, ease of administration, and favorable safety and side effect profile in childhood EoE. The recommended dosage for remission induction is 2x mg/kg body weight per day for omeprazole, with a maximum use of 2 x 40mg/day per os [490]. While there is no drug approval for its use, this is equally lacking for treatment with topical glucocorticoids for childhood.

Recommendation 5.28 (new 2022)

In active EoE without stricture in childhood and adolescence, a 6-food elimination diet, or an elemental diet, or the use of topical corticosteroids may be used alternatively to induce remission (clinically and histologically).

[Recommendation open, strong consensus]

Comment:

The **6-food elimination diet** eliminates the foods most commonly associated with food allergies, i.e. cow's milk proteins, wheat, soy, egg, nuts and fish/seafood. In a retrospective study in children, it was shown that histologic remission was achieved in up to 74% of patients so treated. However, when the individual foods were reintroduced by means of renewed endoscopies, the respective triggering food could only be identified in a few patients [640, 641]. In a prospective study of 50 adult EoE patients, histologic remission (<5 eos/hpf) was achieved in 64% of cases and improvement in symptom score in 95% after a 6-week, 6-food elimination diet [610]. After reintroduction of the food groups, histologic relapse occurred in all cases, matching the initial eosinophil count. In another prospective study of 77 EoE patients, the 6-food elimination diet resulted in histologic remission after 6 weeks in 73% of cases [611]. A meta-analysis published in 2014 found histologic remission rates of 73% in children and 71% in adults after 6-food elimination diet on the basis of 7 studies (4 of which were in children) [642].

The **elemental diet** shows high effectiveness. However, due to the frequent adherence problems, especially in adolescence, its practical usefulness in the treatment of EoE is very limited (see Statement 20).

The remission-inducing effect of topical steroid formulations is very well established (see also Statement 14). Inhaled steroids (e.g. fluticasone), which is sprayed on the tongue and on the back of the throat, budesonide suspensions and recently a budesonide effervescent tablet approved for the treatment of EoE in adults are used.

Application by metered dose inhaler has been shown to have disadvantages in local topical wetting of the esophageal mucosa. A more homogeneous and effective application of the active ingredient budesonide is offered by a suspension of [626]. Application by suspension was first described by Aceves and Dohil [704], the authors prepared a liquid budesonide suspension from sucralose to achieve optimal viscosity. In a retrospectively studied cohort consisting of 20 children with EoE, successful application was demonstrated for the first time [704].

In a follow-up randomized controlled trial with 24 included pediatric patients with EoE, the same authors demonstrated an 87% achievement of histologic remission (<=6 Eos/HPF) after 12 weeks of therapy with a budesonide suspension at a dose of 1-2 mg/day [617].

In another pediatric-only, prospective, placebo-controlled, dose-ranging (0.5, 2, or 4 mg budesonide daily dose) study, Gupta et al. evaluated the efficacy and safety of 12 weeks of treatment with an oral budesonide suspension in 71 children between 2 and 18 years of age [620]. At the end of the 12-week interval, there were significantly more responders in the medium-dose (52.6%) and high-dose (47.1%) oral budesonide groups than in the placebo group (5.6%). The effect was dose-dependent; there was no significant difference in treatment response between the low-dose therapy (11.8%) and the placebo group.

Overall, topical application of oral budesonide suspensions is well tolerated, and treatment adherence is high. However, treatment with glucocorticoids is not free of side effects [565, 567, 621, 705]. A relevant but often subclinical side effect represents esophageal candidiasis in up to 10.5% of adult cases [565, 621]. Prospective studies could observe a systemic effect with consecutive occurrence of adrenal insufficiency in 0-15% of children treated with topical steroids for a long time [619, 705]. Another prospective study in 29 children even detected adrenal suppression in 2/3 of patients 2 weeks after completion of 4 months of therapy with viscous budesonide solution (1 mg/d in children <5 feet and 2 mg in children ≥5 feet body length for 3 months, reduction to half for 1 month and termination) [706]. This implies a relevant suppression of physiologic cortisol levels and thus adverse effects on bone metabolism and body length growth as described for therapy with inhaled glucocorticoids in childhood bronchial asthma should be anticipated [707].

For this reason, topical steroid therapy should be used only as briefly as possible to achieve histologic remission, and the dosage should then be halved to maintenance therapy [571] (e.g., 2x 0.5 mg/d in children > 10 LJ and 2 x 0.25 mg/d in children < 10 LJ). During long-term therapy with oral budesonide suspension in children, it may be considered to determine ACTH and serum cortisol either intermittently or before termination of therapy to detect adrenal insufficiency in a timely manner.

Recommendation 5.29 (new 2022)

In active EoE with stricture, topical corticosteroid therapy should be the primary treatment in children and adolescents to induce remission (clinically and histologically)

[Recommendation, strong consensus]

Comment:

Esophageal strictures can occur in any segment, but are found much more frequently in adults than in pediatric patients [487, 557, 558, 708]. The development of fibrosis to stenosis appears to depend on the duration of the inflammatory state [709]. The complication rate of iatrogenic perforation has leveled off to a value of < 0.1% in the last few years under adherence to a therapeutic safety standard, which includes slow and gradual dilatation [675, 710] Dilatation serves to mechanically remove the stenosis, but the inflammatory process should continue to be treated conservatively (steroids, PPI, nutritional therapy) [710]. Steroids reduce the degree of fibrosis by reducing the number of inflammatory cells [711] as well as the mucosally increased IL-13-mRNA levels in EoE [687]. In addition, it has been shown that the use of topical steroids leads to a reduction in subsequent bolus events [644]. It is further shown that effective control of inflammatory events (e.g., by steroids) results in significantly less dilatation [712]. It is discussed that the responsiveness of patients to topical steroids can be worked out in the future using genomic analysis [619].

Recommendation 5.30

An individualized allergy test-based elimination diet can be implemented in children and adolescents.

[Recommendation open, strong consensus]

Comment:

EoE is commonly found in children and adults with concomitant atopy or atopic predisposition [713, 714]. It is triggered by food allergens and can be triggered by inhalant allergens [715]. Thus, it is not uncommon that a seasonal cluster of initial manifestations of EoE or its clinical exacerbation is often observed in spring. The most common food allergens are found in cow's milk followed by wheat, soy and hen's egg, fish and nuts [713]. Complicating the diagnosis and the identification of the triggering allergen is the fact that especially in young toddlers and school children a polysensitization against the above mentioned food groups can be observed. This means that the trigger of the EoE is mostly caused by 1-3 food allergens and both the individual but also their combination is correspondingly difficult to identify [640, 713, 716].

If adherence problems to a 6FED/elemental diet become apparent at a very early stage, an allergy test-guided individualized elimination diet would be a conceivable therapeutic option. The prick or prick-to-prick skin test has been established as an applied and established allergy testing procedure for the identification of a possible triggering food allergen. By means of this test, the immune responses to the 6 most common food allergens and, if necessary, other anamnestically relevant foods can be investigated by intracutaneous application. However, it is important to mention that the prick test controlled diets are clearly inferior (children 48% and adults 32%) to the alternatives 6FED (children

73%, adults 71%) and elemental diet (children 91%, adults 94%) regarding the achievement of histological remission [642] and has a negative predictive value of only 40-67% (SPT/APT) in a retrospective review of pediatric PPI-nonresponsive patients [671].

A large retrospective pediatric study investigated the value of combined use of prick/patch testing for 23 different food allergens and achieved histologic remission in 72% of treated children after appropriate elimination diets [717]. Subsequent studies in children and adolescents reported response rates of 53-65% using allergy test-targeted elimination diets [717].

However, these observations differ significantly from those in adults. In a prospective study, remission was achieved in only 26% of a collective of 22 adults taking a prick/patch test-based elimination diet [718]. Overall, it can be concluded that prick/patch testing has a high rate of false negative as well as false positive test results, and that for this reason an allergy test-based or -guided elimination diet is generally not recommended. Also, IgE-based allergy test results should not be used for the composition of an individualized elimination diet, since the clinical experience and animal experimental work to date do not point to a significant mechanism in the pathogenesis of EoE, and food-specific IgE elevations can rather be interpreted as sensitization and epiphenomena [518, 641, 719, 720]. There are also no reliable results on the value and classification of the determination of food-specific IgG_2 or IgG_4 subclasses antibodies, their use therefore has no clinical value so far. Only food-specific IgG4 levels seem to be associated with the development of allergy tolerance [720] but also these results need confirmation in further studies.

6 Bibliography

1. Lammert F, Jansen PL, Lerch MM. White Paper Gastroenterology 2020/2021: De Gruyter, 2019.
2. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus. The American Journal of Gastroenterology 2006;101:1900-1920.
3. Judge JE, Rubenstein JH. Presentation and epidemiology of gastroesophageal reflux disease. Gastroenterology 2018;154:267-276.
4. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastroesophageal reflux disease: a systematic review. Gut 2014;63:871-80.
5. Eusebi LH, Ratnakumaran R, Yuan Y, et al. Global prevalence of, and risk factors for, gastroesophageal reflux symptoms: a meta-analysis. Gut 2018;67:430-440.
6. Liu L, Li S, Zhu K, et al. Relationship between esophageal motility and severity of gastroesophageal reflux disease according to the Los Angeles classification. Medicine 2019;98:e15543-e15543.
7. Scida S, Russo M, Miraglia C, et al. Relationship between Helicobacter pylori infection and GERD. Acta Biomed 2018;89:40-43.
8. Becher A, El-Serag H. Systematic review: the association between symptomatic response to proton pump inhibitors and health-related quality of life in patients with gastro-oesophageal reflux disease. Alimentary Pharmacology & Therapeutics 2011;34:618-627.
9. Ness-Jensen E, Gottlieb-Vedi E, Wahlin K, et al. All-cause and cancer-specific mortality in GORD in a population-based cohort study (the HUNT study). Gut 2018;67:209-215.
10. Dent J, Vakil N, Jones R, et al. Accuracy of the diagnosis of GORD by questionnaire, physicians and a trial of proton pump inhibitor treatment: the Diamond Study. Gut 2010;59:714-721.
11. Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: the Lyon Consensus. Gut 2018;67:1351-1362.
12. Rusu RI, Fox MR, Tucker E, et al. Validation of the Lyon classification for GORD diagnosis: acid exposure time assessed by prolonged wireless pH monitoring in healthy controls and patients with erosive esophagitis. Gut 2021;70:2230-2237.
13. Bytzer P, Jones R, Vakil N, et al. Limited Ability of the Proton-Pump Inhibitor Test to Identify Patients With Gastroesophageal Reflux Disease. Clinical Gastroenterology and Hepatology 2012;10:1360-1366.
14. Sifrim D, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. Gut 2012;61:1340-54.
15. Sifrim D, Silny J, Holloway RH, et al. Patterns of gas and liquid reflux during transient lower esophageal sphincter relaxation: a study using intraluminal electrical impedance. Gut 1999;44:47-54.
16. Boeckxstaens GE, Smout A. Systematic review: role of acid, weakly acidic and weakly alkaline reflux in gastroesophageal reflux disease. Alimentary Pharmacology & Therapeutics 2010;32:334-343.
17. Giannini EG, Zentilin P, Dulbecco P, et al. Management Strategy for Patients With Gastroesophageal Reflux Disease: A Comparison Between Empirical Treatment With Esomeprazole and Endoscopy-Oriented Treatment. The American Journal of Gastroenterology 2008;103:267-275.
18. Gerson LB. Diagnostic yield of upper endoscopy in treated GERD patients. Gastroenterology 2010;139:1408-1409.
19. Poh CH, Gasiorowska A, Navarro-Rodriguez T, et al. Upper GI tract findings in patients with heartburn in whom proton pump inhibitor treatment failed versus those not receiving antireflux treatment. Gastrointestinal Endoscopy 2010;71:28-34.
20. Lin EC, Holub J, Lieberman D, et al. Low Prevalence of Suspected Barrett's Esophagus in Patients With Gastroesophageal Reflux Disease Without Alarm Symptoms. Clinical Gastroenterology and Hepatology 2019;17:857-863.
21. García-Altés A, Rota R, Barenys M, et al. Cost-effectiveness of a 'score and scope' strategy for the management of dyspepsia. Eur J Gastroenterol Hepatol 2005;17:709-19.
22. Krishnamoorthi R, Singh S, Ragunathan K, et al. Factors Associated With Progression of Barrett's Esophagus: A Systematic Review and Meta-analysis. Clinical Gastroenterology and Hepatology 2018;16:1046-1055.e8.

23. Codipilly DC, Chandar AK, Singh S, et al. The Effect of Endoscopic Surveillance in Patients With Barrett's Esophagus: A Systematic Review and Meta-analysis. Gastroenterology 2018;154:2068-2086.e5.
24. Sawas T, Killcoyne S, Iyer PG, et al. Identification of Prognostic Phenotypes of Esophageal Adenocarcinoma in 2 Independent Cohorts. Gastroenterology 2018;155:1720-1728.e4.
25. Bennett C, Moayyedi P, Corley DA, et al. BOB CAT: A Large-Scale Review and Delphi Consensus for Management of Barrett's Esophagus With No Dysplasia, Indefinite for, or Low-Grade Dysplasia. The American journal of gastroenterology 2015;110:662-683.
26. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of esophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999;45:172-80.
27. Ismail-Beigi F, Horton PF, Pope CE. Histological Consequences of Gastroesophageal Reflux in Man. Gastroenterology 1970;58:163-174.
28. Fiocca R, Mastracci L, Milione M, et al. Microscopic esophagitis and Barrett's esophagus: The histology report. Digestive and Liver Disease 2011;43:S319-S330.
29. Seefeld U, Krejs GJ, Siebenmann RE, et al. Esophageal histology in gastroesophageal reflux. The American Journal of Digestive Diseases 1977;22:956-964.
30. Collins JSA, Watt PCH, Hamilton PW, et al. Assessment of esophagitis by histology and morphometry. Histopathology 1989;14:381-389.
31. Savarino E, Zentilin P, Mastracci L, et al. Microscopic esophagitis distinguishes patients with non-erosive reflux disease from those with functional heartburn. J Gastroenterol 2013;48:473-82.
32. Kandulski A, Jechorek D, Caro C, et al. Histomorphological differentiation of non-erosive reflux disease and functional heartburn in patients with PPI-refractory heartburn. Alimentary Pharmacology & Therapeutics 2013;38:643-651.
33. Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. Clin Gastroenterol Hepatol 2009;7:1055-61.
34. Mackalski BA, Ilnyckyj A. Esophageal pH testing in patients refractory to proton pump inhibitor therapy. Canadian journal of gastroenterology = Journal canadien de gastroenterologie 2008;22:249-252.
35. Bautista JM, Wong W-m, Pulliam G, et al. The Value of Ambulatory 24 hr Esophageal pH Monitoring in Clinical Practice in Patients Who Were Referred with Persistent Gastroesophageal Reflux Disease (GERD)-Related Symptoms While on Standard Dose Anti-Reflux Medications. Digestive Diseases and Sciences 2005;50:1909-1915.
36. Becker V, Bajbouj M, Waller K, et al. Clinical trial: persistent gastro-oesophageal reflux symptoms despite standard therapy with proton pump inhibitors - a follow-up study of intraluminal-impedance guided therapy. Alimentary Pharmacology & Therapeutics 2007;26:1355-1360.
37. Pritchett JM, Aslam M, Slaughter JC, et al. Efficacy of Esophageal Impedance/pH Monitoring in Patients With Refractory Gastroesophageal Reflux Disease, on and off Therapy. Clinical Gastroenterology and Hepatology 2009;7:743-748.
38. Bajbouj M, Becker V, Phillip V, et al. High-Dose Esomeprazole for Treatment of Symptomatic Refractory Gastroesophageal Reflux Disease – A Prospective pH-Metry/Impedance-Controlled Study. Digestion 2009;80:112-118.
39. Roman S, Gyawali CP, Savarino E, et al. Ambulatory reflux monitoring for diagnosis of gastroesophageal reflux disease: update of the Porto consensus and recommendations from an international consensus group. Neurogastroenterology & Motility 2017;29:e13067.
40. Kline M, Ewing M, Simpson N, et al. The Utility of Intraluminal Impedance in Patients With Gastroesophageal Reflux Disease-Like Symptoms But Normal Endoscopy and 24-Hour pH Testing. Clinical Gastroenterology and Hepatology 2008;6:880-885.
41. Savarino E, Zentilin P, Tutuian R, et al. Impedance-pH reflux patterns can differentiate non-erosive reflux disease from functional heartburn patients. Journal of Gastroenterology 2011;47:159-168.
42. Savarino E, Tutuian R, Zentilin P, et al. Characteristics of Reflux Episodes and Symptom Association in Patients With Erosive Esophagitis and Nonerosive Reflux Disease: Study Using Combined Impedance-pH Off Therapy. American Journal of Gastroenterology 2010;105:1053-1061.

43. Viazis N, Keyoglou A, Kanellopoulos AK, et al. Selective Serotonin Reuptake Inhibitors for the Treatment of Hypersensitive Esophagus: A Randomized, Double-Blind, Placebo-Controlled Study. American Journal of Gastroenterology 2012;107:1662-1667.
44. Ostovaneh MR, Saeidi B, Hajifathalian K, et al. Comparing omeprazole with fluoxetine for treatment of patients with heartburn and normal endoscopy who failed once daily proton pump inhibitors: double-blind placebo-controlled trial. Neurogastroenterology & Motility 2014;26:670-678.
45. Keller J, Fox MR, Allescher HD, et al. [Interpretation and performance of high-resolution esophageal manometry: Recommendations of the German Association of Neurogastroenterology and Motility (DGNM) and the German Association of Gastroenterology, Digestive and Metabolic Diseases (DGVS)]. Z Gastroenterol 2018;56:1378-1408.
46. Pehl C, Keller J, Allescher HD, et al. [Diagnosis of esophageal reflux by PH, impedance, and bilirubin measurement: recommendations of the German Society of Neurogastroenterology and of the working group for neurogastroenterology of the German Society for Digestive and Metabolic Diseases]. Z Gastroenterol 2012;50:1310-32.
47. Yadlapati R. High-resolution esophageal manometry: interpretation in clinical practice. Curr Opin Gastroenterol 2017;33:301-309.
48. Judge JE. Review article: extraoesophageal manifestations of gastro-oesophageal reflux disease. Alimentary Pharmacology and Therapeutics 2005;22:70-80.
49. Yadlapati R, Pandolfino JE, Lidder AK, et al. Oropharyngeal pH Testing Does Not Predict Response to Proton Pump Inhibitor Therapy in Patients with Laryngeal Symptoms. The American journal of gastroenterology 2016;111:1517-1524.
50. Levine MS, Rubesin SE. Diseases of the esophagus: diagnosis with esophagography. Radiology 2005;237:414-427.
51. Baker ME, Rice TW. Radiologic Evaluation of the Esophagus: Methods and Value in Motility Disorders and GERD. Seminars in Thoracic and Cardiovascular Surgery 2001;13:201-225.
52. Ott DJ. Gastroesophageal reflux: what is the role of barium studies? American Journal of Roentgenology 1994;162:627-629.
53. Sellar RJ, de Caestecker JS, Heading RC. Barium radiology: a sensitive test for gastroesophageal reflux. Clinical Radiology 1987;38:303-307.
54. Johnston BT, Troshinsky MB, Castell JA, et al. Comparison of barium radiology with esophageal pH monitoring in the diagnosis of gastroesophageal reflux disease. Am J Gastroenterol 1996;91:1181-5.
55. Thompson JK, Koehler RE, Richter JE. Detection of gastroesophageal reflux: value of barium studies compared with 24-hr pH monitoring. American Journal of Roentgenology 1994;162:621-626.
56. Mariani G, Boni G, Barreca M, et al. Radionuclide gastroesophageal motor studies. J Nucl Med 2004;45:1004-28.
57. Shay SS, Eggli D, Johnson LF. Simultaneous esophageal pH monitoring and scintigraphy during the postprandial period in patients with severe reflux esophagitis. Digestive Diseases and Sciences 1991;36:558-564.
58. Orenstein SR, Klein HA, Rosenthal MS. Scintigraphy versus pH probe for quantification of pediatric gastroesophageal reflux: a study using concurrent multiplexed data and acid feedings. J Nucl Med 1993;34:1228-34.
59. Tolia V, Kuhns L, Kauffman RE. Comparison of simultaneous esophageal pH monitoring and scintigraphy in infants with gastroesophageal reflux. Am J Gastroenterol 1993;88:661-4.
60. Shay SS, Abreu SH, Tsuchida A. Scintigraphy in gastroesophageal reflux disease: a comparison to endoscopy, LESp, and 24-h pH score, as well as to simultaneous pH monitoring. Am J Gastroenterol 1992;87:1094-101.
61. Vandenplas Y, Derde MP, Piepsz A. Evaluation of Reflux Episodes During Simultaneous Esophageal pH Monitoring and Gastroesophageal Reflux Scintigraphy in Children. Journal of Pediatric Gastroenterology and Nutrition 1992;14:256-260.
62. Seibert JJ, Byrne WJ, Euler AR, et al. Gastroesophageal reflux--the acid test: scintigraphy or the pH probe? American Journal of Roentgenology 1983;140:1087-1090.
63. Isaacs PE, Martins JC, Edwards S, et al. Assessment of gastroesophageal reflux disease: comparison of reflux scintigraphy with endoscopy biopsy and esophageal pH monitoring. Hepatogastroenterology 1990;37:198-200.

64. Özcan Z, Özcan C, Erinç R, et al. Scintigraphy in the detection of gastroesophageal reflux in children with caustic esophageal burns: a comparative study with radiography and 24-h pH monitoring. Pediatric Radiology 2001;31:737-741.
65. Kjellén G, Brudin L, Håkansson HO. Is scintigraphy of value in the diagnosis of gastrooesophageal reflux disease? Scand J Gastroenterol 1991;26:425-30.
66. Heyman S, Kirkpatrick JA, Winter HS, et al. An Improved Radionuclide Method for the Diagnosis of Gastroesophageal Reflux and Aspiration in Children (Milk Scan). Radiology 1979;131:479-482.
67. Park J-s, Van Der Wall H, Falk GL. Sa157 CORRELATION OF IMPEDANCE-PH MONITORING AND REFLUX SCINTIGRAPHY RESULTS IN LARYNGOPHARYNGEAL REFLUX DISEASE. Gastroenterology 2021;160:S-442-S-443.
68. Dent J, Brun J, Fendrick AM, et al. An evidence-based appraisal of reflux disease management --- the Genval Workshop Report. Gut 1999;44:S1-S16.
69. Koop H, Schepp W, Müller-Lissner S, et al. Gastroesophageal reflux disease-results of an evidence-based consensus conference of the German Society for Digestive and Metabolic Diseases. Z Gastroenterol 2005;43:163-164.
70 Bytzer P. What Makes Individuals With Gastroesophageal Reflux Disease Dissatisfied With Their Treatment? Clinical Gastroenterology and Hepatology 2009;7:816-822.
71. Junghard O, Carlsson R, Lind T. Sufficient control of heartburn in endoscopy-negative gastro-oesophageal reflux disease trials. Scandinavian Journal of Gastroenterology 2003;38:1197-1199.
72. King A, MacDonald C, Örn C. Understanding gastro-oesophageal reflux disease: a patient-cluster analysis. International Journal of Clinical Practice 2008;62:1838-1843.
73. Castell DO, Kahrilas PJ, Richter JE, et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. The American Journal of Gastroenterology 2002;97:575-583.
74. Labenz J, Armstrong D, Lauritsen K, et al. A randomized comparative study of esomeprazole 40 mg versus pantoprazole 40 mg for healing erosive esophagitis: the EXPO study. Alimentary Pharmacology and Therapeutics 2005;21:739-746.
75. Richter JE, Kahrilas PJ, Johanson J, et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. The American Journal of Gastroenterology 2001;96:656-665.
76. Erichsen R, Robertson D, Farkas DK, et al. Erosive Reflux Disease Increases Risk for Esophageal Adenocarcinoma, Compared With Nonerosive Reflux. Clinical Gastroenterology and Hepatology 2012;10:475-480.e1.
77. Sjostedt S, Befrits R, Sylvan A, et al. Daily treatment with esomeprazole is superior to that taken on-demand for maintenance of healed erosive esophagitis. Alimentary Pharmacology and Therapeutics 2005;22:183-191.
78. El-Serag H, Hill C, Jones R. Systematic review: the epidemiology of gastro-oesophageal reflux disease in primary care, using the UK General Practice Research Database. Alimentary Pharmacology & Therapeutics 2009;29:470-480.
79. Fullard M, Kang JY, Neild P, et al. Systematic review: does gastro-oesophageal reflux disease progress? Alimentary Pharmacology and Therapeutics 2006;24:33-45.
80. Malfertheiner P, Nocon M, Vieth M, et al. Evolution of gastro-oesophageal reflux disease over 5 years under routine medical care--the ProGERD study. Aliment Pharmacol Ther 2012;35:154-64.
81. Ronkainen J, Talley NJ, Storskrubb T, et al. Erosive esophagitis Is a Risk Factor for Barrett's esophagus: A Community-Based Endoscopic Follow-Up Study. American Journal of Gastroenterology 2011;106:1946-1952.
82. Sontag SJ, Sonnenberg A, Schnell TG, et al. The Long-Term Natural History of Gastroesophageal Reflux Disease. Journal of Clinical Gastroenterology 2006;40:398-404.
83. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. New England Journal of Medicine 2011;365:1375-1383.
84. Labenz J, Chandrasoma PT, Knapp LJ, et al. Proposed approach to the challenging management of progressive gastroesophageal reflux disease. World Journal of Gastrointestinal Endoscopy 2018;10:175-183.
85. Willich SN, Nocon M, Kulig M, et al. Cost-of-disease analysis in patients with gastro-oesophageal reflux disease and Barrett's mucosa. Alimentary Pharmacology and Therapeutics 2006;23:371-376.

86. Spechler SJ. Proton pump inhibitors. Medical Clinics of North America 2019;103:1-14.
87. Lin D, Eke C, Cai C, et al. Decreasing Overall and Inappropriate Proton Pump Inhibitor Use: Perspective From a Large Safety-Net Healthcare System. Clinical Gastroenterology and Hepatology 2020;18:763-766.e2.
88. Labenz J, Armstrong D, Leodolter A, et al. Management of reflux esophagitis: does the choice of proton pump inhibitor matter? International Journal of Clinical Practice 2015;69:796-801.
89. Vaezi MF, Sifrim D. Assessing Old and New Diagnostic Tests for Gastroesophageal Reflux Disease. Gastroenterology 2018;154:289-301.
90. Spechler SJ, Hunter JG, Jones KM, et al. Randomized Trial of Medical versus Surgical Treatment for Refractory Heartburn. N Engl J Med 2019;381:1513-1523.
91. Hampel H, Abraham NS, El-Serag HB. Meta-Analysis: Obesity and the Risk for Gastroesophageal Reflux Disease and Its Complications. Annals of Internal Medicine 2005;143:199.
92. Pandolfino JE, El-Serag HB, Zhang Q, et al. Obesity: A Challenge to Esophagogastric Junction Integrity. Gastroenterology 2006;130:639-649.
93. Pandolfino JE, Kwiatek MA, Kahrilas PJ. The pathophysiologic basis for epidemiologic trends in gastroesophageal reflux disease. Gastroenterol Clin North Am 2008;37:827-43, viii.
94. Wu JCY, Mui LM, Cheung CMY, et al. Obesity Is Associated With Increased Transient Lower Esophageal Sphincter Relaxation. Gastroenterology 2007;132:883-889.
95. Kaltenbach T, Crockett S, Gerson LB. Are Lifestyle Measures Effective in Patients With Gastroesophageal Reflux Disease? Archives of Internal Medicine 2006;166:965.
96. Ness-Jensen E, Hveem K, El-Serag H, et al. Lifestyle Intervention in Gastroesophageal Reflux Disease. Clinical Gastroenterology and Hepatology 2016;14:175-182.e3.
97. Ness-Jensen E, Lindam A, Lagergren J, et al. Weight Loss and Reduction in Gastroesophageal Reflux. A Prospective Population-Based Cohort Study: the HUNT Study. American Journal of Gastroenterology 2013;108:376-382.
98. Katz PO, Gerson LB, Vela MF. Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. American Journal of Gastroenterology 2013;108:308-328.
99. Allampati S, Lopez R, Thota PN, et al. Use of a positional therapy device significantly improves nocturnal gastroesophageal reflux symptoms. Diseases of the Esophagus 2016.
100. Casale M, Sabatino L, Moffa A, et al. Breathing training on lower esophageal sphincter as a complementary treatment of gastroesophageal reflux disease (GERD): a systematic review. Eur Rev Med Pharmacol Sci 2016;20:4547-4552.
101. Mitchell DR, Derakhshan MH, Wirz AA, et al. Abdominal Compression by Waist Belt Aggravates Gastroesophageal Reflux, Primarily by Impairing Esophageal Clearance. Gastroenterology 2017;152:1881-1888.
102. Johnson T, Gerson L, Hershcovici T, et al. Systematic review: the effects of carbonated beverages on gastroesophageal reflux disease. Alimentary Pharmacology & Therapeutics 2010;31:607-614.
103. Mehta RS, Song M, Staller K, et al. Association Between Beverage Intake and Incidence of Gastroesophageal Reflux Symptoms. Clinical Gastroenterology and Hepatology 2020;18:2226-2233.e4.
104. Newberry C, Lynch K. The role of diet in the development and management of gastroesophageal reflux disease: why we feel the burn. Journal of Thoracic Disease 2019;11:S1594-S1601.
105. Triadafilopoulos G, Korzilius JW, Zikos T, et al. Ninety-Six Hour Wireless Esophageal pH Study in Patients with GERD Shows that Restrictive Diet Reduces Esophageal Acid Exposure. Digestive Diseases and Sciences 2019;65:2331-2344.
106. Schey R, Dickman R, Parthasarathy S, et al. Sleep Deprivation Is Hyperalgesic in Patients With Gastroesophageal Reflux Disease. Gastroenterology 2007;133:1787-1795.
107. Herregods TVK, van Hoeij FB, Oors JM, et al. Effect of Running on Gastroesophageal Reflux and Reflux Mechanisms. American Journal of Gastroenterology 2016;111:940-946.
108. Morgner-Miehlke A, Koop H, Blum A, et al. Clarification and therapy of reflux complaints. Journal of Gastroenterology 2006;44:399-410.
109. Kulig M, Nocon M, Vieth M, et al. Risk factors of gastroesophageal reflux disease: methodology and first epidemiological results of the ProGERD study. Journal of Clinical Epidemiology 2004;57:580-589.

110. Dent J, Becher A, Sung J, et al. Systematic Review: Patterns of Reflux-Induced Symptoms and Esophageal Endoscopic Findings in Large-Scale Surveys. Clinical Gastroenterology and Hepatology 2012;10:863-873.e3.
111. Norman Hansen A, Bergheim R, Fagertun H, et al. A randomised prospective study comparing the effectiveness of esomeprazole treatment strategies in clinical practice for 6 months in the management of patients with symptoms of gastroesophageal reflux disease. International Journal of Clinical Practice 2005;59:665-671.
112. Howden CW, Henning JM, Huang B, et al. Management of heartburn in a large, randomized, community-based study: comparison of four therapeutic strategies. The American Journal of Gastroenterology 2001;96:1704-1710.
113. van Pinxteren B, Sigterman KE, Bonis P, et al. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd, 2010.
114. Pouchain D, Bigard M-A, Liard F, et al. Gaviscon® vs. omeprazole in symptomatic treatment of moderate gastroesophageal reflux. a direct comparative randomised trial. BMC Gastroenterology 2012;12.
115. Gyawali CP, Fass R. Management of Gastroesophageal Reflux Disease. Gastroenterology 2018;154:302-318.
116. Leiman DA, Riff BP, Morgan S, et al. Alginate therapy is effective treatment for GERD symptoms: a systematic review and meta-analysis. Diseases of the Esophagus 2017;30:1-9.
117. Spechler SJ. Evaluation and Treatment of Patients with Persistent Reflux Symptoms Despite Proton Pump Inhibitor Treatment. Gastroenterology Clinics of North America 2020;49:437-450.
118. Labenz J, Koop H. Gastroesophageal reflux disease-what to do when PPIs are not sufficiently effective, tolerated, or desired? DMW - Deutsche Medizinische Wochenschrift 2017;142:356-366.
119. Kirchheiner J, Glatt S, Fuhr U, et al. Relative potency of proton-pump inhibitors-comparison of effects on intragastric pH. European Journal of Clinical Pharmacology 2008;65:19-31.
120. Armstrong D, Talley NJ, Lauritsen K, et al. The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with esomeprazole or omeprazole. Alimentary Pharmacology & Therapeutics 2004;20:413-421.
121. Labenz J, Morgner-Miehlke A. An update on the available treatments for non-erosive reflux disease. Expert Opinion on Pharmacotherapy 2005;7:47-56.
122. Dean BB, Gano AD, Knight K, et al. Effectiveness of proton pump inhibitors in nonerosive reflux disease. Clinical Gastroenterology and Hepatology 2004;2:656-664.
123. Weijenborg PW, Cremonini F, Smout AJ, et al. PPI therapy is equally effective in well-defined non-erosive reflux disease and in reflux esophagitis: a meta-analysis. Neurogastroenterol Motil 2012;24:747-57, e350.
124. Watson RG, Tham TC, Johnston BT, et al. Double blind cross-over placebo controlled study of omeprazole in the treatment of patients with reflux symptoms and physiological levels of acid reflux--the "sensitive esophagus". Gut 1997;40:587-590.
125. Farré R, Fornari F, Blondeau K, et al. Acid and weakly acidic solutions impair mucosal integrity of distally exposed and proximally non-exposed human oesophagus. Gut 2009;59:164-169.
126. Matthews PJ, Knowles CH, Chua YC, et al. Effects of the concentration and frequency of acid infusion on the development and maintenance of esophageal hyperalgesia in a human volunteer model. American Journal of Physiology-Gastrointestinal and Liver Physiology 2008;294:G914-G917.
127. Cremonini F, Ziogas DC, Chang HY, et al. Meta-analysis: the effects of placebo treatment on gastro-oesophageal reflux disease. Alimentary Pharmacology & Therapeutics 2010;32:29-42.
128. Khan M, Santana J, Donnellan C, et al. Medical treatments in the short term management of reflux oesophagitis. Cochrane Database Syst Rev 2007:Cd003244.
129. Weijenborg PW, de Schepper HS, Smout AJPM, et al. Effects of Antidepressants in Patients With Functional Esophageal Disorders or Gastroesophageal Reflux Disease: A Systematic Review. Clinical Gastroenterology and Hepatology 2015;13:251-259.e1.
130. Chen W-Y, Chang W-L, Tsai Y-C, et al. Double-Dosed Pantoprazole Accelerates the Sustained Symptomatic Response in Overweight and Obese Patients With Reflux Esophagitis in Los Angeles Grades A and B. American Journal of Gastroenterology 2010;105:1046-1052.
131. Chiba N, De Gara CJ, Wilkinson JM, et al. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: A meta-analysis. Gastroenterology 1997;112:1798-1810.

132. Katz PO, Johnson DA, Levine D, et al. A model of healing of Los Angeles grades C and D reflux oesophagitis: is there an optimal time of acid suppression for maximal healing? Alimentary Pharmacology & Therapeutics 2010;32:443-447.
133. Edwards SJ, Lind T, Lundell L, et al. Systematic review: standard- and double-dose proton pump inhibitors for the healing of severe erosive esophagitis - a mixed treatment comparison of randomized controlled trials. Alimentary Pharmacology & Therapeutics 2009;30:547-556.
134. Hsu P-I, Lu C-L, Wu D-C, et al. Eight Weeks of Esomeprazole Therapy Reduces Symptom Relapse, Compared With 4 Weeks, in Patients With Los Angeles Grade A or B Erosive Esophagitis. Clinical Gastroenterology and Hepatology 2015;13:859-866.e1.
135. Gralnek IM, Dulai GS, Fennerty MB, et al. Esomeprazole Versus Other Proton Pump Inhibitors in Erosive Esophagitis: A Meta-Analysis of Randomized Clinical Trials. Clinical Gastroenterology and Hepatology 2006;4:1452-1458.
136. Moayyedi P, Delaney B. GORD in adults. BMJ Clin Evid 2008;2008.
137. Katzka DA, Pandolfino JE, Kahrilas PJ. Phenotypes of Gastroesophageal Reflux Disease: where Rome, Lyon, and Montreal Meet. Clinical Gastroenterology and Hepatology 2020;18:767-776.
138. Armstrong D, Veldhuyzen van Zanten SJO, Barkun AN, et al. Heartburn-dominant, uninvestigated dyspepsia: a comparison of 'PPI-start' and 'H2-RA-start' management strategies in primary care - the CADET-HR Study. Alimentary Pharmacology and Therapeutics 2005;21:1189-1202.
139. Cho JH, Shin CM, Yoon H, et al. Efficacy of a high-dose proton pump inhibitor in patients with gastroesophageal reflux disease: a single center, randomized, open-label trial. BMC Gastroenterology 2020;20.
140. Fass R, Sontag SJ, Traxler B, et al. Treatment of Patients With Persistent Heartburn Symptoms: A Double-Blind, Randomized Trial. Clinical Gastroenterology and Hepatology 2006;4:50-56.
141. Miner P, Katz PO, Chen Y, et al. Gastric Acid Control With Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, and Rabeprazole: A Five-Way Crossover Study. American Journal of Gastroenterology 2003;98:2616-2620.
142. Manabe N, Haruma K, Ito M, et al. Efficacy of adding sodium alginate to omeprazole in patients with nonerosive reflux disease: a randomized clinical trial. Diseases of the Esophagus 2011;25:373-380.
143. Reimer C, Lødrup AB, Smith G, et al. Randomised clinical trial: alginate (Gaviscon Advance) vs. placebo as add-on therapy in reflux patients with inadequate response to a once daily proton pump inhibitor. Alimentary Pharmacology & Therapeutics 2016;43:899-909.
144. Müller M, Labenz G, Borkenstein D-P, et al. Alginate on demand as an add-on in case of insufficient effect of proton pump inhibitors in patients with gastroesophageal reflux disease. DMW - Deutsche Medizinische Wochenschrift 2018;144:e30-e35.
145. Coyle C, Crawford G, Wilkinson J, et al. Randomised clinical trial: addition of alginate-antacid (Gaviscon Double Action) to proton pump inhibitor therapy in patients with breakthrough symptoms. Alimentary Pharmacology & Therapeutics 2017;45:1524-1533.
146. Labenz J, Gross M. Reflux disease beyond PPIs. MMW - Advances in Medicine 2018;160:40-44.
147. Yadlapati R, Vaezi MF, Vela MF, et al. Management options for patients with GERD and persistent symptoms on proton pump inhibitors: recommendations from an expert panel. Am J Gastroenterol 2018;113:980-986.
148. Hungin APS, Molloy-Bland M, Scarpignato C. Revisiting Montreal: New Insights into Symptoms and Their Causes, and Implications for the Future of GERD. American Journal of Gastroenterology 2018;114:414-421.
149. Fuchs KH, Musial F, Ulbricht F, et al. Foregut symptoms, somatoform tendencies, and the selection of patients for antireflux surgery. Dis Esophagus 2017;30:1-10.
150. Graham DY, Tansel A. Interchangeable use of proton pump inhibitors based on relative potency. Clinical Gastroenterology and Hepatology 2018;16:800-808.e7.
151. Kessing BF, Bredenoord AJ, Smout AJ. Erroneous diagnosis of gastroesophageal reflux disease in achalasia. Clin Gastroenterol Hepatol 2011;9:1020-4.
152 Bösner S, Haasenritter J, Becker A, et al. Heartburn or angina? Differentiating gastrointestinal disease in primary care patients presenting with chest pain: a cross sectional diagnostic study. International Archives of Medicine 2009;2:40.
153. Labenz J, Labenz C. Gastroenterological diseases as triggers of chest pain. Der Internist 2016;58:29-38.

154. Schmulson MJ, Drossman DA. What Is New in Rome IV. Journal of Neurogastroenterology and Motility 2017;23:151-163.
155. Bell RCW. Management of regurgitation in patients with gastroesophageal reflux disease. Current Opinion in Gastroenterology 2020;36:336-343.
156. Kahrilas PJ, Howden CW, Hughes N. Response of regurgitation to proton pump inhibitor therapy in clinical trials of gastroesophageal reflux disease. American Journal of Gastroenterology 2011;106:1419-1425.
157. Kahrilas PJ, Jonsson A, Denison H, et al. Regurgitation Is Less Responsive to Acid Suppression Than Heartburn in Patients With Gastroesophageal Reflux Disease. Clinical Gastroenterology and Hepatology 2012;10:612-619.
158. Kahrilas PJ, Howden CW, Wernersson B, et al. Impact of persistent, frequent regurgitation on quality of life in heartburn responders treated with acid suppression: a multinational primary care study. Alimentary Pharmacology & Therapeutics 2013;37:1005-1010.
159. Armstrong D. Systematic review: persistence and severity in gastroesophageal reflux disease. Aliment Pharmacol Ther 2008;28:841-53.
160. Modlin IM, Hunt RH, Malfertheiner P, et al. Diagnosis and Management of Non-Erosive Reflux Disease – The Vevey NERD Consensus Group. Digestion 2009;80:74-88.
161. Khan Z, Alastal Y, Khan MA, et al. On-demand Therapy with Proton Pump Inhibitors for Maintenance Treatment of Nonerosive Reflux Disease or Mild Erosive Esophagitis: A Systematic Review and Meta-Analysis. Gastroenterology Research and Practice 2018;2018:1-10.
162. Metz DC, Inadomi JM, Howden CW, et al. On-demand therapy for gastroesophageal reflux disease. The American Journal of Gastroenterology 2007;102:642-653.
163. Pace F, Tonini M, Pallotta S, et al. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken â˜on-demandâ™. Alimentary Pharmacology & Therapeutics 2007;26:195-204.
164. Ronkainen J, Aro P, Storskrubb T, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: A Kalixanda study report. Scandinavian Journal of Gastroenterology 2005;40:275-285.
165. Johnson DA, Benjamin SB, Vakil NB, et al. Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: a randomized, double-blind, placebo-controlled study of efficacy and safety. The American Journal of Gastroenterology 2001;96:27-34.
166. Vakil NB, Shaker R, Johnson DA, et al. The new proton pump inhibitor esomeprazole is effective as a maintenance therapy in GERD patients with healed erosive esophagitis: a 6-month, randomized, double-blind, placebo-controlled study of efficacy and safety. Alimentary Pharmacology & Therapeutics 2001;15:927-935.
167. Targownik L. Discontinuing Long-Term PPI Therapy: Why, With Whom, and How? American Journal of Gastroenterology 2018;113:519-528.
168. Cloud ML, Enas N, Humphries TJ, et al. Rabeprazole in treatment of acid peptic diseases: results of three placebo-controlled dose-response clinical trials in duodenal ulcer, gastric ulcer, and gastroesophageal reflux disease (GERD). The Rabeprazole Study Group. Dig Dis Sci 1998;43:993-1000.
169. Earnest DL, Dorsch E, Jones J, et al. A Placebo-Controlled Dose-Ranging Study of Lansoprazole in the Management of Reflux Esophagitis. American Journal of Gastroenterology 1998;93:238-243.
170. Labenz J, Armstrong D, Lauritsen K, et al. Esomeprazole 20 mg vs. pantoprazole 20 mg for maintenance therapy of healed erosive esophagitis: results from the EXPO study1. Alimentary Pharmacology and Therapeutics 2005;22:803-811.
171. Lauritsen K, Devière J, Bigard MA, et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. Alimentary Pharmacology & Therapeutics 2003;17:333-341.
172. Caos A, Breiter J, Perdomo C, et al. Long-term prevention of erosive or ulcerative gastroesophageal reflux disease relapse with rabeprazole 10 or 20 mg vs. placebo: results of a 5-year study in the United States. Alimentary Pharmacology and Therapeutics 2005;22:193-202.
173. Johnson DA, Katz PO, Levine D, et al. Prevention of Relapse of Healed Reflux Esophagitis is Related to the Duration of Intragastric pH>4. Journal of Clinical Gastroenterology 2010;44:475-478.

174. Desai M, Hamade N, Sharma P. Management of peptic strictures. American Journal of Gastroenterology 2020;115:967-970.
175. Vaezi MF, Katzka D, Zerbib F. Extraesophageal Symptoms and Diseases Attributed to GERD: Where is the Pendulum Swinging Now? Clinical Gastroenterology and Hepatology 2018;16:1018-1029.
176. Kahrilas PJ, Howden CW, Hughes N, et al. Response of Chronic Cough to Acid-Suppressive Therapy in Patients With Gastroesophageal Reflux Disease. Chest 2013;143:605-612.
177. Kiljander TO, Harding SM, Field SK, et al. Effects of esomeprazole 40 mg Twice Daily on asthma. American Journal of Respiratory and Critical Care Medicine 2006;173:1091-1097.
178. Durazzo M, Lupi G, Cicerchia F, et al. Extra-esophageal presentation of gastroesophageal reflux disease: 2020 update. Journal of Clinical Medicine 2020;9:2559.
179. Lam PKY, Ng ML, Cheung TK, et al. Rabeprazole Is Effective in Treating Laryngopharyngeal Reflux in a Randomized Placebo-Controlled Trial. Clinical Gastroenterology and Hepatology 2010;8:770-776.
180. Vaezi MF, Richter JE, Stasney CR, et al. Treatment of Chronic Posterior Laryngitis With Esomeprazole. The Laryngoscope 2006;116:254-260.
181. Lechien JR, Saussez S, Schindler A, et al. Clinical outcomes of laryngopharyngeal reflux treatment: a systematic review and meta-analysis. The Laryngoscope 2018;129:1174-1187.
182. Bajbouj M, Becker V, Eckel F, et al. Argon Plasma Coagulation of Cervical Heterotopic Gastric Mucosa as an Alternative Treatment for Globus Sensations. Gastroenterology 2009;137:440-444.
183. Tseng W-H, Tseng P-H, Wu J-F, et al. Double-blind, placebo-controlled study with alginate suspension for laryngopharyngeal reflux disease. The Laryngoscope 2018;128:2252-2260.
184. Cremonini F, Wise J, Moayyedi P, et al. Diagnostic and Therapeutic Use of Proton Pump Inhibitors in Non-Cardiac Chest Pain: A Metaanalysis. The American Journal of Gastroenterology 2005;100:1226-1232.
185. Wang WH, Huang JQ, Zheng GF, et al. Is Proton Pump Inhibitor Testing an Effective Approach to Diagnose Gastroesophageal Reflux Disease in Patients With Noncardiac Chest Pain? Archives of Internal Medicine 2005;165:1222.
186. Kim JH, Sinn DH, Son HJ, et al. Comparison of one-week and two-week empirical trial with a high-dose rabeprazole in non-cardiac chest pain patients. Journal of Gastroenterology and Hepatology 2009;24:1504-1509.
187. Hershcovici T, Achem SR, Jha LK, et al. Systematic review: the treatment of noncardiac chest pain. Alimentary Pharmacology & Therapeutics 2011;35:5-14.
188. Flook NW, Moayyedi P, Dent J, et al. Acid-Suppressive Therapy With Esomeprazole for Relief of Unexplained Chest Pain in Primary Care: A Randomized, Double-Blind, Placebo-Controlled Trial. American Journal of Gastroenterology 2013;108:56-64.
189. Kahrilas PJ, Hughes N, Howden CW. Response of unexplained chest pain to proton pump inhibitor treatment in patients with and without objective evidence of gastroesophageal reflux disease. Gut 2011;60:1473-8.
190. Talwar V, Wurm P, Bankart MJG, et al. Clinical trial: chest pain caused by presumed gastro-oesophageal reflux in coronary artery disease - controlled study of lansoprazole vs. placebo. Alimentary Pharmacology & Therapeutics 2010;32:191-199.
191. Kim Y, Ganocy S, Fass R. Proton-pump inhibitor use and the development of new ischemic heart disease in non-cardiac chest pain patients. Neurogastroenterology & Motility 2020;32.
192. George N, Abdallah J, Maradey-Romero C, et al. Review article: the current treatment of non-cardiac chest pain. Alimentary Pharmacology & Therapeutics 2015;43:213-239.
193. Jung H-k, Choung RS, Talley NJ. Gastroesophageal reflux disease and sleep disorders: evidence for a causal link and therapeutic implications. Journal of Neurogastroenterology and Motility 2010;16:22-29.
194. Dent J, Holloway RH, Eastwood PR. Systematic review: relationships between sleep and gastroesophageal reflux. Alimentary Pharmacology & Therapeutics 2013;38:657-673.
195. Shepherd K, Ockelford J, Ganasan V, et al. Temporal Relationship Between Night-Time Gastroesophageal Reflux Events and Arousals From Sleep. American Journal of Gastroenterology 2020;115:697-705.
196. Regenbogen E, Helkin A, Georgopoulos R, et al. Esophageal Reflux Disease Proton Pump Inhibitor Therapy Impact on Sleep Disturbance. Otolaryngology-Head and Neck Surgery 2012;146:524-532.

197. Orr WC, Craddock A, Goodrich S. Acidic and Non-Acidic Reflux During Sleep Under Conditions of Powerful Acid Suppression. Chest 2007;131:460-465.
198. Moayyedi P, Hunt R, Armstrong D, et al. The impact of intensifying acid suppression on sleep disturbance related to gastro-oesophageal reflux disease in primary care. Alimentary Pharmacology & Therapeutics 2013;37:730-737.
199. Nocon M, Labenz J, Jaspersen D, et al. Health-related quality of life in patients with gastro-oesophageal reflux disease under routine care: 5-year follow-up results of the ProGERD study. Alimentary Pharmacology & Therapeutics 2009;29:662-668.
200. Gagliardi GS, Shah AP, Goldstein M, et al. Effect of zolpidem on the sleep arousal response to nocturnal esophageal acid exposure. Clinical Gastroenterology and Hepatology 2009;7:948-952.
201. Orr WC. Review article: sleep-related gastroesophageal reflux as a distinct clinical entity. Alimentary Pharmacology & Therapeutics 2010;31:47-56.
202. Deraman MA, Abdul Hafidz MI, Lawenko RM, et al. Randomised clinical trial: the effectiveness of Gaviscon Advance vs non-alginate antacid in suppression of acid pocket and post-prandial reflux in obese individuals after late-night supper. Alimentary Pharmacology & Therapeutics 2020;51:1014-1021.
203. Ali RAR, Egan LJ. Gastroesophageal reflux disease in pregnancy. Best Practice & Research Clinical Gastroenterology 2007;21:793-806.
204. Thélin CS, Richter JE. Review article: the management of heartburn during pregnancy and lactation. Alimentary Pharmacology & Therapeutics 2020;51:421-434.
205. Fill Malfertheiner S, Malfertheiner MV, Kropf S, et al. A prospective longitudinal cohort study: evolution of GERD symptoms during the course of pregnancy. BMC Gastroenterology 2012;12.
206. Larson J, Patatanian E, Minerjr P, et al. Double-blind, placebo-controlled study of ranitidine for gastroesophageal reflux symptoms during pregnancy. Obstetrics & Gynecology 1997;90:83-87.
207. Fill S, Malfertheiner M, Costa SD, et al. Management of gastroesophageal reflux disease (GERD) in pregnancy. Journal of obstetrics and neonatology 2007;211:215-223.
208 Majithia R, Johnson DA. Are proton pump inhibitors safe during pregnancy and lactation? Drugs 2012;72:171-179.
209. Judge JE. Review article: the management of heartburn in pregnancy. Alimentary Pharmacology and Therapeutics 2005;22:749-757.
210. Tytgat GN, Heading RC, Müller-Lissner S, et al. Contemporary understanding and management of reflux and constipation in the general population and pregnancy: a consensus meeting. Alimentary Pharmacology & Therapeutics 2003;18:291-301.
211. van der Woude CJ, Metselaar HJ, Danese S. Management of gastrointestinal and liver diseases during pregnancy. Gut 2014;63:1014-1023.
212. Strugala V, Bassin J, Swales VS, et al. Assessment of the Safety and Efficacy of a Raft-Forming Alginate Reflux Suppressant (Liquid Gaviscon) for the Treatment of Heartburn during Pregnancy. ISRN Obstetrics and Gynecology 2012;2012:1-6.
213. Petersen K-U, Labenz J. Location 2010. digestive diseases 2010, 2010.
214. Gill SK, O'Brien L, Einarson TR, et al. The Safety of Proton Pump Inhibitors (PPIs) in Pregnancy: A Meta-Analysis. The American Journal of Gastroenterology 2009;104:1541-1545.
215. Pasternak B, Hviid A. Use of Proton-Pump Inhibitors in Early Pregnancy and the Risk of Birth Defects. New England Journal of Medicine 2010;363:2114-2123.
216. Matok I, Levy A, Wiznitzer A, et al. The Safety of Fetal Exposure to Proton-Pump Inhibitors During Pregnancy. Digestive Diseases and Sciences 2011;57:699-705.
217. Mitchell AA. Proton pump inhibitors and birth defects-Some reassurance, but more needed. New England Journal of Medicine 2010;363:2161-2163.
218. Koop H. Prescribing practices and risks of proton pump blockers-fiction and facts. Journal of Gastroenterology 2018;56:264-274.
219. Donnellan C, Preston C, Moayyedi P, et al. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd, 2004.
220. Labenz J, Labenz C. Prevalence and natural history of gastroesophageal reflux disease. The Gastroenterologist 2016;11:102-109.
221. Ford AC, Forman D, Bailey AG, et al. The natural history of gastroesophageal reflux symptoms in the community and its effects on survival: a longitudinal 10-year follow-up study. Alimentary Pharmacology & Therapeutics 2012;37:323-331.

222. Boghossian TA, Rashid FJ, Thompson W, et al. Deprescribing versus continuation of chronic proton pump inhibitor use in adults. Cochrane Database of Systematic Reviews 2017.
223. Ruigómez A, Alberto García Rodríguez L, Wallander M-A, et al. Esophageal stricture: incidence, treatment patterns, and recurrence rate. The American Journal of Gastroenterology 2006;101:2685-2692.
224. Reimer C, Søndergaard B, Hilsted L, et al. Proton-Pump Inhibitor Therapy Induces Acid-Related Symptoms in Healthy Volunteers After Withdrawal of Therapy. Gastroenterology 2009;137:80-87.e1.
225. Metz DC, Pilmer BL, Han C, et al. Withdrawing PPI Therapy After Healing Esophagitis Does Not Worsen Symptoms or Cause Persistent Hypergastrinemia: Analysis of Dexlansoprazole MR Clinical Trial Data. American Journal of Gastroenterology 2011;106:1953-1960.
226. Bjornsson E, Abrahamsson H, Simren M, et al. Discontinuation of proton pump inhibitors in patients on long-term therapy: a double-blind, placebo-controlled trial. Alimentary Pharmacology and Therapeutics 2006;24:945-954.
227. El-Omar EM, Banerjee S, Wirz AA, et al. Marked rebound acid hypersecretion after treatment with ranitidine. The American journal of gastroenterology 1996;91 2:355-9.
228. Coyle C, Symonds R, Allan J, et al. Sustained proton pump inhibitor deprescribing among dyspeptic patients in general practice: a return to self-management through a programme of education and alginate rescue therapy. A prospective interventional study. BJGP Open 2019;3:bjgpopen19X101651.
229. Farrell B, Pottie K, Thompson W, et al. Deprescribing proton pump inhibitors: evidence-based clinical practice guideline. Can Fam Physician 2017;63:354-364.
230. Yadlapati R, Masihi M, Gyawali CP, et al. Ambulatory Reflux Monitoring Guides Proton Pump Inhibitor Discontinuation in Patients With Gastroesophageal Reflux Symptoms: A Clinical Trial. Gastroenterology 2021;160:174-182.e1.
231. Corley DA. Safety and Complications of Long-Term Proton Pump Inhibitor Therapy: Getting Closer to the Truth. Gastroenterology 2019;157:604-607.
232. Ueberschaer H, Allescher H-D. Proton pump inhibitors - side effects and complications of long-term proton pump inhibitor use. Journal of Gastroenterology 2017;55:63-74.
233. Vaezi MF, Yang Y-X, Howden CW. Complications of proton pump inhibitor therapy. Gastroenterology 2017;153:35-48.
234. Attwood SE, Ell C, Galmiche JP, et al. Long-term safety of proton pump inhibitor therapy assessed under controlled, randomised clinical trial conditions: data from the SOPRAN and LOTUS studies. Alimentary Pharmacology & Therapeutics 2015;41:1162-1174.
235. Moayyedi P, Eikelboom JW, Bosch J, et al. Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin. Gastroenterology 2019;157:682-691.e2.
236. Lochhead P, Hagan K, Joshi AD, et al. Association Between Proton Pump Inhibitor Use and Cognitive Function in Women. Gastroenterology 2017;153:971-979.e4.
237. Wod M, Hallas J, Andersen K, et al. Lack of Association Between Proton Pump Inhibitor Use and Cognitive Decline. Clinical Gastroenterology and Hepatology 2018;16:681-689.
238. Desai M, Nutalapati V, Srinivasan S, et al. Proton pump inhibitors do not increase the risk of dementia: a systematic review and meta-analysis of prospective studies. Diseases of the Esophagus 2020;33.
239. Targownik LE. Editorial: let's take a break from studying the PPI-fracture association. Alimentary Pharmacology & Therapeutics 2018;47:1543-1544.
240. Hoff M, Skovlund E, Skurtveit S, et al. Proton pump inhibitors and fracture risk. The HUNT study, Norway. Osteoporosis International 2019;31:109-118.
241. Kumar S, Drake MT, Schleck CD, et al. Incidence and predictors of osteoporotic fractures in patients with Barrett's esophagus: a population-based nested case-control study. Alimentary Pharmacology & Therapeutics 2017;46:1094-1102.
242. Targownik LE. Editorial: Non-breaking news! High-dose PPIs likely do not cause fractures. Alimentary Pharmacology & Therapeutics 2017;47:137-137.
243. Targownik LE, Goertzen AL, Luo Y, et al. Long-Term Proton Pump Inhibitor Use Is Not Associated With Changes in Bone Strength and Structure. American Journal of Gastroenterology 2017;112:95-101.
244. Targownik LE, Leslie WD, Davison SK, et al. The Relationship Between Proton Pump Inhibitor Use and Longitudinal Change in Bone Mineral Density: A Population-Based From the Canadian

Multicentre Osteoporosis Study (CaMos). American Journal of Gastroenterology 2012;107:1361-1369.
245. Hansen KE, Nieves JW, Nudurupati S, et al. Dexlansoprazole and Esomeprazole Do Not Affect Bone Homeostasis in Healthy Postmenopausal Women. Gastroenterology 2019;156:926-934.e6.
246. Lee JK, Merchant SA, Schneider JL, et al. Proton Pump Inhibitor Use and Risk of Gastric, Colorectal, Liver, and Pancreatic Cancers in a Community-Based Population. American Journal of Gastroenterology 2020;115:706-715.
247. Ghosh G, Schnoll-Sussman F, Mathews S, et al. Reported proton pump inhibitor side effects: what are physician and patient perspectives and behavior patterns? Alimentary Pharmacology & Therapeutics 2019;51:121-128.
248. Kurlander JE, Kennedy JK, Rubenstein JH, et al. Patients' Perceptions of Proton Pump Inhibitor Risks and Attempts at Discontinuation: A National Survey. American Journal of Gastroenterology 2019;114:244-249.
249. Kurlander JE, Rubenstein JH, Richardson CR, et al. Physicians' Perceptions of Proton Pump Inhibitor Risks and Recommendations to Discontinue: A National Survey. American Journal of Gastroenterology 2020;115:689-696.
250. Fischbach W, Malfertheiner P, Lynen Jansen P, et al [S2k-guideline Helicobacter pylori and gastroduodenal ulcer disease]. Z Gastroenterol 2016;54:327-63.
251. Lundell L, Vieth M, Gibson F, et al. Systematic review: the effects of long-term proton pump inhibitor use on serum gastrin levels and gastric histology. Alimentary Pharmacology & Therapeutics 2015;42:649-663.
252. Cheung KS, Chan EW, Wong AYS, et al. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. Gut 2017;67:28-35.
253. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut 2017;66:6-30.
254. Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr 2018;66:516-554.
255. Smith JA, Decalmer S, Kelsall A, et al. Acoustic cough-reflux associations in chronic cough: potential triggers and mechanisms. Gastroenterology 2010;139:754-62.
256. Kaufman JA, Houghland JE, Quiroga E, et al. Long-term outcomes of laparoscopic antireflux surgery for gastroesophageal reflux disease (GERD)-related airway disorder. Surg Endosc 2006;20:1824-30.
257. DeMeester TR, Bonavina L, Albertucci M. Nissen fundoplication for gastroesophageal reflux disease. Evaluation of primary repair in 100 consecutive patients. Ann Surg 1986;204:9-20.
258. Hill LD, Kozarek RA, Kraemer SJ, et al. The gastroesophageal flap valve: in vitro and in vivo observations. Gastrointest Endosc 1996;44:541-7.
259. Fuchs KH, Freys SM, Heimbucher J, et al. Pathophysiologic spectrum in patients with gastroesophageal reflux disease in a surgical GI-function laboratory. Diseases of the Esophagus 1995;8:211-217.
260. Tack J, Pandolfino JE. Pathophysiology of gastroesophageal reflux disease. Gastroenterology 2018;154:277-288.
261. Costantini M, Crookes PF, Bremner RM, et al. Value of physiologic assessment of foregut symptoms in a surgical practice. Surgery 1993;114:780-6; discussion 786-7.
262. Raman A, Sternbach J, Babajide A, et al. When does testing for GERD become cost effective in an integrated health network? Surg Endosc 2010;24:1245-9.
263. Chan WW, Haroian LR, Gyawali CP. Value of preoperative esophageal function studies before laparoscopic antireflux surgery. Surg Endosc 2011;25:2943-9.
264. Bredenoord AJ, Weusten BL, Timmer R, et al. Characteristics of gastroesophageal reflux in symptomatic patients with and without excessive esophageal acid exposure. Am J Gastroenterol 2006;101:2470-5.
265. Hemmink GJ, Bredenoord AJ, Weusten BL, et al. Esophageal pH-impedance monitoring in patients with therapy-resistant reflux symptoms: 'on' or 'off' proton pump inhibitor? Am J Gastroenterol 2008;103:2446-53.

266. Roman S, Gyawali CP, Savarino E, et al. Ambulatory reflux monitoring for diagnosis of gastroesophageal reflux disease: update of the Porto consensus and recommendations from an international consensus group. Neurogastroenterol Motil 2017;29:1-15.
267. Jobe BA, Richter JE, Hoppo T, et al. Preoperative diagnostic workup before antireflux surgery: an evidence and experience-based consensus of the Esophageal Diagnostic Advisory Panel. J Am Coll Surg 2013;217:586-97.
268. Salvatore S, Hauser B, Vandemaele K, et al. Gastroesophageal reflux disease in infants: how much is predictable with questionnaires, pH-metry, endoscopy and histology? J Pediatr Gastroenterol Nutr 2005;40:210-5.
269. Funderburk A, Nawab U, Abraham S, et al. Temporal Association Between Reflux-like Behaviors and Gastroesophageal Reflux in Preterm and Term Infants. J Pediatr Gastroenterol Nutr 2016;62:556-61.
270. Zaninotto G, DeMeester TR, Schwizer W, et al. The lower esophageal sphincter in health and disease. Am J Surg 1988;155:104-11.
271. Kahrilas PJ, Sifrim D. High-resolution manometry and impedance-pH/manometry: valuable tools in clinical and investigational esophagology. Gastroenterology 2008;135:756-69.
272. Lord RV, DeMeester SR, Peters JH, et al. Hiatal hernia, lower esophageal sphincter incompetence, and effectiveness of Nissen fundoplication in the spectrum of gastroesophageal reflux disease. J Gastrointest Surg 2009;13:602-10.
273. Kahrilas PJ, Bredenoord AJ, Carlson DA, et al. Advances in Management of Esophageal Motility Disorders. Clin Gastroenterol Hepatol 2018;16:1692-1700.
274. Kahrilas PJ, Bredenoord AJ, Fox M, et al. Expert consensus document: advances in the management of esophageal motility disorders in the era of high-resolution manometry: a focus on achalasia syndromes. Nat Rev Gastroenterol Hepatol 2017;14:677-688.
275. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil 2015;27:160-74.
276. Gyawali CP, Roman S, Bredenoord AJ, et al. Classification of esophageal motor findings in gastroesophageal reflux disease: conclusions from an international consensus group. Neurogastroenterol Motil 2017;29.
277. Kuster E, Ros E, Toledo-Pimentel V, et al. Predictive factors of the long term outcome in gastro-oesophageal reflux disease: six year follow up of 107 patients. Gut 1994;35:8-14.
278. Fein M, Bueter M, Thalheimer A, et al. Ten-year outcome of laparoscopic antireflux surgery. J Gastrointest Surg 2008;12:1893-9.
279. Campos GM, Peters JH, DeMeester TR, et al. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. J Gastrointest Surg 1999;3:292-300.
280. Stein HJ, Barlow AP, DeMeester TR, et al. Complications of gastroesophageal reflux disease. Role of the lower esophageal sphincter, esophageal acid and acid/alkaline exposure, and duodenogastric reflux. Ann Surg 1992;216:35-43.
281. Kamolz T, Granderath F, Pointner R. Laparoscopic antireflux surgery: disease-related quality of life assessment before and after surgery in GERD patients with and without Barrett's esophagus. Surg Endosc 2003;17:880-5.
282. Dallemagne B, Weerts J, Markiewicz S, et al. Clinical results of laparoscopic fundoplication at ten years after surgery. Surg Endosc 2006;20:159-65.
283. Broeders JA, Draaisma WA, Bredenoord AJ, et al. Impact of symptom-reflux association analysis on long-term outcome after Nissen fundoplication. Br J Surg 2011;98:247-54.
284. Mehta S, Bennett J, Mahon D, et al. Prospective trial of laparoscopic nissen fundoplication versus proton pump inhibitor therapy for gastroesophageal reflux disease: seven-year follow-up. J Gastrointest Surg 2006;10:1312-6; discussion 1316-7.
285. Anvari M, Allen C, Marshall J, et al. A randomized controlled trial of laparoscopic Nissen fundoplication versus proton pump inhibitors for the treatment of patients with chronic gastroesophageal reflux disease (GERD): 3-year outcomes. Surg Endosc 2011;25:2547-54.
286. Galmiche JP, Hatlebakk J, Attwood S, et al. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. JAMA 2011;305:1969-77.
287 Pauwels A, Boecxstaens V, Andrews CN, et al. How to select patients for antireflux surgery? The ICARUS guidelines (international consensus regarding preoperative examinations and clinical characteristics assessment to select adult patients for antireflux surgery). Gut 2019;68:1928-1941.

288. Gonzalez Ayerbe JI, Hauser B, Salvatore S, et al. Diagnosis and Management of Gastroesophageal Reflux Disease in Infants and Children: from Guidelines to Clinical Practice. Pediatr Gastroenterol Hepatol Nutr 2019;22:107-121.
289. Lightdale JR, Gremse DA, Section on Gastroenterology H, et al. Gastroesophageal reflux: management guidance for the pediatrician. Pediatrics 2013;131:e1684-95.
290. Maret-Ouda J, Yanes M, Konings P, et al. Mortality from laparoscopic antireflux surgery in a nationwide cohort of the working-age population. Br J Surg 2016;103:863-70.
291. Yanes M, Santoni G, Maret-Ouda J, et al. Mortality, Reoperation, and Hospital Stay Within 90 Days of Primary and Secondary Antireflux Surgery in a Population-Based Multinational Study. Gastroenterology 2021;160:2283-2290.
292. Funk LM, Kanji A, Scott Melvin W, et al. Elective antireflux surgery in the US: an analysis of national trends in utilization and inpatient outcomes from 2005 to 2010. Surg Endosc 2014;28:1712-9.
293. Granderath FA, Kamolz T, Schweiger UM, et al [Outcome after laparoscopic antireflux surgery: fundoplication and re-fundoplication in the elderly]. Surgeon 2001;72:1026-31.
294. Kamolz T, Granderath FA, Pointner R. Does major depression in patients with gastroesophageal reflux disease affect the outcome of laparoscopic antireflux surgery? Surg Endosc 2003;17:55-60.
295. Kamolz T, Bammer T, Granderath FA, et al. Laparoscopic antireflux surgery in gastroesophageal reflux disease patients with concomitant anxiety disorders. Dig Liver Dis 2001;33:659-64.
296. Fuchs HF, Babic B, Fuchs KH, et al. Do patients with gastroesophageal reflux disease and somatoform tendencies benefit from antireflux surgery? World J Gastroenterol 2019;25:388-397.
297. Broeders JA, Draaisma WA, Bredenoord AJ, et al. Long-term outcome of Nissen fundoplication in non-erosive and erosive gastro-oesophageal reflux disease. Br J Surg 2010;97:845-52.
298. Fuchs KH, Breithaupt W, Varga G, et al. Primary laparoscopic fundoplication in selected patients with gastroesophageal reflux disease. Dis Esophagus 2021.
299. Grant AM, Wileman SM, Ramsay CR, et al. Minimal access surgery compared with medical management for chronic gastro-oesophageal reflux disease: UK collaborative randomised trial. BMJ 2008;337:a2664.
300. Salminen PT, Hiekkanen HI, Rantala AP, et al. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. Ann Surg 2007;246:201-6.
301. Broeders JA, Rijnhart-de Jong HG, Draaisma WA, et al. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. Ann Surg 2009;250:698-706.
302. Rothenberg SS. Two decades of experience with laparoscopic nissen fundoplication in infants and children: a critical evaluation of indications, technique, and results. J Laparoendosc Adv Surg Tech A 2013;23:791-4.
303. Laws HL, Clements RH, Swillie CM. A randomized, prospective comparison of the Nissen fundoplication versus the Toupet fundoplication for gastroesophageal reflux disease. Ann Surg 1997;225:647-53; discussion 654.
304. Huerta CT, Plymale M, Barrett P, et al. Long-term efficacy of laparoscopic Nissen versus Toupet fundoplication for the management of types III and IV hiatal hernias. Surg Endosc 2019;33:2895-2900.
305. Watson DI, Jamieson GG, Pike GK, et al. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. Br J Surg 1999;86:123-30.
306. Fibbe C, Layer P, Keller J, et al. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. Gastroenterology 2001;121:5-14.
307. Baigrie RJ, Cullis SN, Ndhluni AJ, et al. Randomized double-blind trial of laparoscopic Nissen fundoplication versus anterior partial fundoplication. Br J Surg 2005;92:819-23.
308. Spence GM, Watson DI, Jamiesion GG, et al. Single center prospective randomized trial of laparoscopic Nissen versus anterior 90 degrees fundoplication. J Gastrointest Surg 2006;10:698-705.
309. Guerin E, Betroune K, Closset J, et al. Nissen versus Toupet fundoplication: results of a randomized and multicenter trial. Surg Endosc 2007;21:1985-90.

310 Engstrom C, Lonroth H, Mardani J, et al. An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. World J Surg 2007;31:1221-5; discussion 1226-7.
311. Mickevicius A, Endzinas Z, Kiudelis M, et al. Influence of wrap length on the effectiveness of Nissen and Toupet fundoplication: a prospective randomized study. Surg Endosc 2008;22:2269-76.
312. Mickevicius A, Endzinas Z, Kiudelis M, et al. Influence of wrap length on the effectiveness of Nissen and Toupet fundoplications: 5-year results of prospective, randomized study. Surg Endosc 2013;27:986-91.
313. Booth MI, Stratford J, Jones L, et al. Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastroesophageal reflux disease based on preoperative esophageal manometry. Br J Surg 2008;95:57-63.
314. Strate U, Emmermann A, Fibbe C, et al. Laparoscopic fundoplication: Nissen versus Toupet two-year outcome of a prospective randomized study of 200 patients regarding preoperative esophageal motility. Surg Endosc 2008;22:21-30.
315. Nijjar RS, Watson DI, Jamieson GG, et al. Five-year follow-up of a multicenter, double-blind randomized clinical trial of laparoscopic Nissen vs anterior 90 degrees partial fundoplication. Arch Surg 2010;145:552-7.
316. Cao Z, Cai W, Qin M, et al. Randomized clinical trial of laparoscopic anterior 180 degrees partial versus 360 degrees Nissen fundoplication: 5-year results. Dis Esophagus 2012;25:114-20.
317. Shaw JM, Bornman PC, Callanan MD, et al. Long-term outcome of laparoscopic Nissen and laparoscopic Toupet fundoplication for gastroesophageal reflux disease: a prospective, randomized trial. Surg Endosc 2010;24:924-32.
318. Catarci M, Gentileschi P, Papi C, et al. Evidence-based appraisal of antireflux fundoplication. Ann Surg 2004;239:325-37.
319. Neufeld M, Graham A. Levels of evidence available for techniques in antireflux surgery. Dis Esophagus 2007;20:161-7.
320. Davis CS, Baldea A, Johns JR, et al. The evolution and long-term results of laparoscopic antireflux surgery for the treatment of gastroesophageal reflux disease. JSLS 2010;14:332-41.
321. Fein M, Seyfried F. Is there a role for anything other than a Nissen's operation? J Gastrointest Surg 2010;14 Suppl 1:S67-74.
322. Broeders JA, Mauritz FA, Ahmed Ali U, et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg 2010;97:1318-30.
323. Tan G, Yang Z, Wang Z. Meta-analysis of laparoscopic total (Nissen) versus posterior (Toupet) fundoplication for gastroesophageal reflux disease based on randomized clinical trials. ANZ J Surg 2011;81:246-52.
324. Horvath KD, Jobe BA, Herron DM, et al. Laparoscopic Toupet fundoplication is an inadequate procedure for patients with severe reflux disease. J Gastrointest Surg 1999;3:583-91.
325. Patti MG, Robinson T, Galvani C, et al. Total fundoplication is superior to partial fundoplication even when esophageal peristalsis is weak. J Am Coll Surg 2004;198:863-9; discussion 869-70.
326. Fuchs KH, Breithaupt W, Fein M, et al. Laparoscopic Nissen repair: indications, techniques and long-term benefits. Langenbecks Arch Surg 2005;390:197-202.
327. Morgenthal CB, Shane MD, Stival A, et al. The durability of laparoscopic Nissen fundoplication: 11-year outcomes. J Gastrointest Surg 2007;11:693-700.
328. Sgromo B, Irvine LA, Cuschieri A, et al. Long-term comparative outcome between laparoscopic total Nissen and Toupet fundoplication: symptomatic relief, patient satisfaction and quality of life. Surg Endosc 2008;22:1048-53.
329. Watson DI, Jamieson GG, Lally C, et al. Multicenter, prospective, double-blind, randomized trial of laparoscopic nissen vs anterior 90 degrees partial fundoplication. Arch Surg 2004;139:1160-7.
330. Ayazi S, Chowdhury N, Zaidi AH, et al. Magnetic sphincter augmentation (MSA) in patients with hiatal hernia: clinical outcome and patterns of recurrence. Surg Endosc 2020;34:1835-1846.
331. Ganz RA, Peters JH, Horgan S. Esophageal sphincter device for gastroesophageal reflux disease. N Engl J Med 2013;368:2039-40.
332. Schizas D, Mastoraki A, Papoutsi E, et al. LINX((R)) reflux management system to bridge the "treatment gap" in gastroesophageal reflux disease: A systematic review of 35 studies. World J Clin Cases 2020;8:294-305.

333. Dunn C, Bildzukewicz N, Lipham J. Magnetic sphincter augmentation for gastroesophageal reflux disease. Gastrointest Endosc Clin N Am 2020;30:325-342.
334. Rathore MA, Andrabi SI, Bhatti MI, et al. Metaanalysis of recurrence after laparoscopic repair of paraesophageal hernia. JSLS 2007;11:456-60.
335. Eypasch E, Thiel B, Sauerland S. Laparoscopic fundoplication for gastro-oesophageal reflux disease - a consensus development conference and the evidence-based benefit. Langenbecks Arch Surg 2000;385:57-63.
336. Fuchs KH, Feussner H, Bonavina L, et al. Current status and trends in laparoscopic antireflux surgery: results of a consensus meeting. The European Study Group for Antireflux Surgery (ESGARS). Endoscopy 1997;29:298-308.
337. Lundell L, Miettinen P, Myrvold HE, et al. Continued (5-year) follow-up of a randomized clinical study comparing antireflux surgery and omeprazole in gastroesophageal reflux disease. J Am Coll Surg 2001;192:172-9; discussion 179-81.
338. Lundell L, Attwood S, Ell C, et al. Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastroesophageal reflux disease: a 3-year interim analysis of the LOTUS trial. Gut 2008;57:1207-13.
339. Chew CR, Jamieson GG, Devitt PG, et al. Prospective randomized trial of laparoscopic Nissen fundoplication with anterior versus posterior hiatal repair: late outcomes. World J Surg 2011;35:2038-44.
340. Antoniou SA, Antoniou GA, Koch OO, et al. Lower recurrence rates after mesh-reinforced versus simple hiatal hernia repair: a meta-analysis of randomized trials. Surg Laparosc Endosc Percutan Tech 2012;22:498-502.
341. Asti E, Sironi A, Bonitta G, et al. Crura augmentation with Bio-A(®) mesh for laparoscopic repair of hiatal hernia: single-institution experience with 100 consecutive patients. Hernia 2017;21:623-628.
342. Balagué C, Fdez-Ananín S, Sacoto D, et al. Paraesophageal Hernia: To Mesh or Not to Mesh? The Controversy Continues. J Laparoendosc Adv Surg Tech A 2020;30:140-146.
343. Keville S, Rabach L, Saad AR, et al. Evolution From the U-shaped to Keyhole-shaped Mesh Configuration in the Repair of Paraesophageal and Recurrent Hiatal Hernia. Surg Laparosc Endosc Percutan Tech 2020;30:339-344.
344. Koetje JH, Oor JE, Roks DJ, et al. Equal patient satisfaction, quality of life and objective recurrence rate after laparoscopic hiatal hernia repair with and without mesh. Surg Endosc 2017;31:3673-3680.
345. Oor JE, Roks DJ, Koetje JH, et al. Randomized clinical trial comparing laparoscopic hiatal hernia repair using sutures versus sutures reinforced with non-absorbable mesh. Surg Endosc 2018;32:4579-4589.
346. Watson DI, Thompson SK, Devitt PG, et al. Five Year Follow-up of a Randomized Controlled Trial of Laparoscopic Repair of Very Large Hiatus Hernia With Sutures Versus Absorbable Versus Nonabsorbable Mesh. Ann Surg 2020;272:241-247.
347. Frantzides CT, Madan AK, Carlson MA, et al. A prospective, randomized trial of laparoscopic polytetrafluoroethylene (PTFE) patch repair vs simple cruroplasty for large hiatal hernia. Arch Surg 2002;137:649-52.
348. Granderath FA, Schweiger UM, Kamolz T, et al. Laparoscopic Nissen fundoplication with prosthetic hiatal closure reduces postoperative intrathoracic wrap herniation: preliminary results of a prospective randomized functional and clinical study. Arch Surg 2005;140:40-8.
349. Muller-Stich BP, Linke GR, Senft J, et al. Laparoscopic Mesh-augmented Hiatoplasty With Cardiophrenicopexy Versus Laparoscopic Nissen Fundoplication for the Treatment of Gastroesophageal Reflux Disease: A Double-center Randomized Controlled Trial. Ann Surg 2015;262:721-5; discussion 725-7.
350. Soricelli E, Basso N, Genco A, et al. Long-term results of hiatal hernia mesh repair and antireflux laparoscopic surgery. Surg Endosc 2009;23:2499-504.
351. Stadlhuber RJ, Sherif AE, Mittal SK, et al. Mesh complications after prosthetic reinforcement of hiatal closure: a 28-case series. Surg Endosc 2009;23:1219-26.
352. Parker M, Bowers SP, Bray JM, et al. Hiatal mesh is associated with major resection at revisional surgery. Surg Endosc 2010;24:3095-101.
353. Mehta S, Boddy A, Rhodes M. Review of outcome after laparoscopic paraesophageal hiatal hernia repair. Surg Laparosc Endosc Percutan Tech 2006;16:301-6.
354. Pallabazzer G, Santi S, Parise P, et al. Giant hiatal hernias: direct hiatus closure has an acceptable recurrence rate. Updates Surg 2011;63:75-81.

355. Furnee EJ, Draaisma WA, Gooszen HG, et al. Tailored or routine addition of an antireflux fundoplication in laparoscopic large hiatal hernia repair: a comparative cohort study. World J Surg 2011;35:78-84.
356. Yano F, Stadlhuber RJ, Tsuboi K, et al. Outcomes of surgical treatment of intrathoracic stomach. Dis Esophagus 2009;22:284-8.
357. Youssef YK, Shekar N, Lutfi R, et al. Long-term evaluation of patient satisfaction and reflux symptoms after laparoscopic fundoplication with Collis gastroplasty. Surg Endosc 2006;20:1702-5.
358. Mattioli S, Lugaresi ML, Costantini M, et al. The short esophagus: intraoperative assessment of esophageal length. J Thorac Cardiovasc Surg 2008;136:834-41.
359. Lugaresi M, Mattioli B, Daddi N, et al. Surgery for type III-IV hiatal hernia: anatomical recurrence and global results after elective treatment of short esophagus with open and minimally invasive surgery. Eur J Cardiothorac Surg 2016;49:1137-43.
360. Lugaresi M, Mattioli B, Daddi N, et al. True Short Esophagus in Gastro-esophageal Reflux Disease: Old Controversies With New Perspectives. Ann Surg 2019.
361. Zehetner J, DeMeester SR, Ayazi S, et al. Laparoscopic wedge fundectomy for collis gastroplasty creation in patients with a foreshortened esophagus. Ann Surg 2014;260:1030-3.
362. Maret-Ouda J, Wahlin K, El-Serag HB, et al. Association Between Laparoscopic Antireflux Surgery and Recurrence of Gastroesophageal Reflux. JAMA 2017;318:939-946.
363. Csendes A, Orellana O, Cuneo N, et al. Long-term (15-year) objective evaluation of 150 patients after laparoscopic Nissen fundoplication. Surgery 2019;166:886-894.
364. Zhou T, Harnsberger C, Broderick R, et al. Reoperation rates after laparoscopic fundoplication. Surg Endosc 2015;29:510-4.
365. Baerg J, Thorpe D, Bultron G, et al. A multicenter study of the incidence and factors associated with redo Nissen fundoplication in children. J Pediatr Surg 2013;48:1306-11.
366. Al Hashmi AW, Pineton de Chambrun G, Souche R, et al. A retrospective multicenter analysis on redo-laparoscopic anti-reflux surgery: conservative or conversion fundoplication? Surg Endosc 2019;33:243-251.
367. Del Campo SEM, Mansfield SA, Suzo AJ, et al. Laparoscopic redo fundoplication improves disease-specific and global quality of life following failed laparoscopic or open fundoplication. Surg Endosc 2017;31:4649-4655.
368. Wykypiel H, Kamolz T, Steiner P, et al. Austrian experiences with redo antireflux surgery. Surg Endosc 2005;19:1315-9.
369. Iqbal A, Awad Z, Simkins J, et al. Repair of 104 failed anti-reflux operations. Ann Surg 2006;244:42-51.
370. Oelschlager BK, Lal DR, Jensen E, et al. Medium- and long-term outcome of laparoscopic redo fundoplication. Surg Endosc 2006;20:1817-23.
371. Khajanchee YS, O'Rourke R, Cassera MA, et al. Laparoscopic reintervention for failed antireflux surgery: subjective and objective outcomes in 176 consecutive patients. Arch Surg 2007;142:785-901; discussion 791-2.
372. Cowgill SM, Arnaoutakis D, Villadolid D, et al. "Redo" fundoplications: satisfactory symptomatic outcomes with higher cost of care. J Surg Res 2007;143:183-8.
373. Funch-Jensen P, Bendixen A, Iversen MG, et al. Complications and frequency of redo antireflux surgery in Denmark: a nationwide study, 1997-2005. Surg Endosc 2008;22:627-30.
374. Furnee EJ, Draaisma WA, Broeders IA, et al. Surgical reintervention after failed antireflux surgery: a systematic review of the literature. J Gastrointest Surg 2009;13:1539-49.
375. Dallemagne B, Arenas Sanchez M, Francart D, et al. Long-term results after laparoscopic reoperation for failed antireflux procedures. Br J Surg 2011;98:1581-7.
376. Schlottmann F, Laxague F, Angeramo CA, et al. Outcomes of Laparoscopic Redo Fundoplication in Patients With Failed Antireflux Surgery: A Systematic Review and Meta-analysis. Ann Surg 2021;274:78-85.
377. Vilar A, Priego P, Puerta A, et al. Redo surgery after failure of antireflux surgery. Am Surg 2018;84:1819-1824.
378. Varban OA, McCoy TP, Westcott C. A comparison of pre-operative comorbidities and post-operative outcomes among patients undergoing laparoscopic nissen fundoplication at high- and low-volume centers. J Gastrointest Surg 2011;15:1121-7.
379. Wilshire CL, Louie BE, Shultz D, et al. Clinical Outcomes of Reoperation for Failed Antireflux Operations. Ann Thorac Surg 2016;101:1290-6.

380. Gatenby PA, Ramus JR, Caygill CP, et al. Relevance of the detection of intestinal metaplasia in non-dysplastic columnar-lined esophagus. Scand J Gastroenterol 2008;43:524-30.
381. Kelty CJ, Gough MD, Van Wyk Q, et al. Barrett's oesophagus: intestinal metaplasia is not essential for cancer risk. Scand J Gastroenterol 2007;42:1271-4.
382. Playford RJ. New British Society of Gastroenterology (BSG) guidelines for the diagnosis and management of Barrett's oesophagus. Gut 2006;55:442.
383. Srivastava A, Odze RD, Lauwers GY, et al. Morphologic features are useful in distinguishing Barrett's esophagus from carditis with intestinal metaplasia. Am J Surg Pathol 2007;31:1733-41.
384. Naini BV, Souza RF, Odze RD. Barrett's esophagus: A Comprehensive and Contemporary Review for Pathologists. Am J Surg Pathol 2016;40:e45-66.
385. Yousef F, Cardwell C, Cantwell MM, et al. The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. Am J Epidemiol 2008;168:237-49.
386. Takubo K, Aida J, Naomoto Y, et al. Cardiac rather than intestinal-type background in endoscopic resection specimens of minute Barrett's adenocarcinoma. Human Pathology 2009;40:65-74.
387. Chandrasoma P, Wijetunge S, DeMeester S, et al. Columnar-Lined Esophagus Without Intestinal Metaplasia Has No Proven Risk of Adenocarcinoma. American Journal of Surgical Pathology 2012;36:1-7.
388. Westerhoff M, Hovan L, Lee C, et al. Effects of Dropping the Requirement for Goblet Cells From the Diagnosis of Barrett's Esophagus. Clinical Gastroenterology and Hepatology 2012;10:1232-1236.
389. Thomas T, Abrams KR, De Caestecker JS, et al. Meta analysis: cancer risk in Barrett's oesophagus. Alimentary Pharmacology & Therapeutics 2007;26:1465-1477.
390. Alcedo J, Ferrández A, Arenas J, et al. Trends in Barrett's esophagus diagnosis in Southern Europe: implications for surveillance. Diseases of the Esophagus 2009;22:239-248.
391. Anaparthy R, Gaddam S, Kanakadandi V, et al. Association Between Length of Barrett's Esophagus and Risk of High-grade Dysplasia or Adenocarcinoma in Patients Without Dysplasia. Clinical Gastroenterology and Hepatology 2013;11:1430-1436.
392. Sharma P, Dent J, Armstrong D, et al. The Development and Validation of an Endoscopic Grading System for Barrett's Esophagus: The Prague C & M Criteria. Gastroenterology 2006;131:1392-1399.
393. Pech O, Gossner L, Manner H, et al. Prospective evaluation of the macroscopic types and location of early Barrett's neoplasia in 380 lesions. Endoscopy 2007;39:588-593.
394. Peters FP, Brakenhoff KPM, Curvers WL, et al. Histologic evaluation of resection specimens obtained at 293 endoscopic resections in Barrett's esophagus. Gastrointestinal Endoscopy 2008;67:604-609.
395. Bisschops R, Areia M, Coron E, et al. Performance measures for upper gastrointestinal endoscopy: A European Society of Gastrointestinal Endoscopy quality improvement initiative. United European Gastroenterology Journal 2016;4:629-656.
396. McClave SA, Worth Boyce H, Gottfried MR. Early diagnosis of columnar-lined esophagus: a new endoscopic diagnostic criterion. Gastrointestinal Endoscopy 1987;33:413-416.
397. Singh S, Garg SK, Singh PP, et al. Acid-suppressive medications and risk of esophageal adenocarcinoma in patients with Barrett's esophagus: a systematic review and meta-analysis. Gut 2013;63:1229-1237.
398. Souza RF, Shewmake K, Terada LS, et al. Acid exposure activates the mitogen-activated protein kinase pathways in Barrett's esophagus. Gastroenterology 2002;122:299-307.
399. Clemons NJ, McColl KEL, Fitzgerald RC. Nitric Oxide and Acid Induce Double-Strand DNA Breaks in Barrett's Esophagus Carcinogenesis via Distinct Mechanisms. Gastroenterology 2007;133:1198-1209.
400. Jankowski JAZ, de Caestecker J, Love SB, et al. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. Lancet 2018;392:400-408.
401. Nguyen T, Khalaf N, Ramsey D, et al. Statin Use Is Associated With a Decreased Risk of Barrett's Esophagus. Gastroenterology 2014;147:314-323.
402. Nguyen T, Duan Z, Naik AD, et al. Statin Use Reduces Risk of Esophageal Adenocarcinoma in US Veterans With Barrett's Esophagus: A Nested Case-Control Study. Gastroenterology 2015;149:1392-1398.

403. Gupta N, Gaddam S, Wani SB, et al. Longer inspection time is associated with increased detection of high-grade dysplasia and esophageal adenocarcinoma in Barrett's esophagus. Gastrointestinal Endoscopy 2012;76:531-538.
404. Levine DS, Haggitt RC, Blount PL, et al. An endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus. Gastroenterology 1993;105:40-50.
405. Peters FP, Curvers WL, Rosmolen WD, et al. Surveillance history of endoscopically treated patients with early Barrett's neoplasia: nonadherence to the Seattle biopsy protocol leads to sampling error. Diseases of the Esophagus 2008;21:475-479.
406. Abela J-E, Going JJ, Mackenzie JF, et al. Systematic Four-Quadrant Biopsy Detects Barrett's Dysplasia in More Patients Than Nonsystematic Biopsy. The American Journal of Gastroenterology 2008;103:850-855.
407. Canto MI, Yoshida T, Gossner L. Chromoscopy of intestinal metaplasia in Barrett's esophagus. Endoscopy 2002;34:330-336.
408. Yuki T, Amano Y, Kushiyama Y, et al. Evaluation of modified crystal violet chromoendoscopy procedure using new mucosal pit pattern classification for detection of Barrett's dysplastic lesions. Digestive and Liver Disease 2006;38:296-300.
409. Guelrud M, Herrera I, Essenfeld H, et al. Enhanced magnification endoscopy: A new technique to identify specialized intestinal metaplasia in Barrett's esophagus. Gastrointestinal Endoscopy 2001;53:559-565.
410. Sharma P. Magnification chromoendoscopy for the detection of intestinal metaplasia and dysplasia in Barrett's oesophagus. Gut 2003;52:24-27.
411. Coletta M, Sami SS, Nachiappan A, et al. Acetic acid chromoendoscopy for the diagnosis of early neoplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. Gastrointestinal Endoscopy 2016;83:57-67.e1.
412. Qumseya BJ, Wang H, Badie N, et al. Advanced Imaging Technologies Increase Detection of Dysplasia and Neoplasia in Patients With Barrett's Esophagus: A Meta-analysis and Systematic Review. Clinical Gastroenterology and Hepatology 2013;11:1562-1570.e2.
413. Desai TK, Krishnan K, Samala N, et al. The incidence of esophageal adenocarcinoma in non-dysplastic Barrett's esophagus: a meta-analysis. Gut 2012;61:970-6.
414. Haidry RJ, Dunn JM, Butt MA, et al. Radiofrequency Ablation and Endoscopic Mucosal Resection for Dysplastic Barrett's Esophagus and Early Esophageal Adenocarcinoma: Outcomes of the UK National Halo RFA Registry. Gastroenterology 2013;145:87-95.
415. Gupta M, Iyer PG, Lutzke L, et al. Recurrence of Esophageal Intestinal Metaplasia After Endoscopic Mucosal Resection and Radiofrequency Ablation of Barrett's Esophagus: Results From a US Multicenter Consortium. Gastroenterology 2013;145:79-86.e1.
416. Kerkhof M, van Dekken H, Steyerberg EW, et al. Grading of dysplasia in Barrett's oesophagus: substantial interobserver variation between general and gastrointestinal pathologists. Histopathology 2007;50:920-927.
417. Pech O, Vieth M, Schmitz D, et al. Conclusions from the histological diagnosis of low-grade intraepithelial neoplasia in Barrett's oesophagus. Scandinavian Journal of Gastroenterology 2007;42:682-688.
418. Curvers WL, ten Kate FJ, Krishnadath KK, et al. Low-grade dysplasia in Barrett's esophagus: Overdiagnosed and Underestimated. American Journal of Gastroenterology 2010;105:1523-1530.
419. Duits LC, Phoa KN, Curvers WL, et al. Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. Gut 2014;64:700-706.
420. Wani S, Falk G, Hall M, et al. Patients With Nondysplastic Barrett's Esophagus Have Low Risks for Developing Dysplasia or Esophageal Adenocarcinoma. Clinical Gastroenterology and Hepatology 2011;9:220-227.e1.
421. Duits LC, van der Wel MJ, Cotton CC, et al. Patients With Barrett's Esophagus and Confirmed Persistent Low-Grade Dysplasia Are at Increased Risk for Progression to Neoplasia. Gastroenterology 2017;152:993-1001.e1.
422. Qumseya BJ, Wani S, Gendy S, et al. Disease Progression in Barrett's Low-Grade Dysplasia With Radiofrequency Ablation Compared With Surveillance: Systematic Review and Meta-Analysis. American Journal of Gastroenterology 2017;112:849-865.

423. Pouw RE, Klaver E, Phoa KN, et al. Radiofrequency ablation for low-grade dysplasia in Barrett's esophagus: long-term outcome of a randomized trial. Gastrointestinal Endoscopy 2020;92:569-574.
424. Pech O, Bollschweiler E, Manner H, et al. Comparison Between Endoscopic and Surgical Resection of Mucosal Esophageal Adenocarcinoma in Barrett's Esophagus At Two High-Volume Centers. Annals of Surgery 2011;254:67-72.
425. Prasad GA, Wu TT, Wigle DA, et al. Endoscopic and Surgical Treatment of Mucosal (T1a) Esophageal Adenocarcinoma in Barrett's Esophagus. Gastroenterology 2009;137:815-823.
426. Pech O, May A, Manner H, et al. Long-term Efficacy and Safety of Endoscopic Resection for Patients With Mucosal Adenocarcinoma of the Esophagus. Gastroenterology 2014;146:652-660.e1.
427. Phoa KN, Pouw RE, Bisschops R, et al. Multimodality endoscopic eradication for neoplastic Barrett's oesophagus: results of an European multicentre study (EURO-II). Gut 2015;65:555-562.
428. Pouw RE, Beyna T, Belghazi K, et al. A prospective multicenter study using a new multiband mucosectomy device for endoscopic resection of early neoplasia in Barrett's esophagus. Gastrointestinal Endoscopy 2018;88:647-654.
429. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) position statement. Endoscopy 2017;49:191-198.
430. Probst A, Aust D, Märkl B, et al. Early esophageal cancer in Europe: endoscopic treatment by endoscopic submucosal dissection. Endoscopy 2014;47:113-121.
431. Wu J, Pan Y-m, Wang T-t, et al. Endotherapy versus surgery for early neoplasia in Barrett's esophagus: a meta-analysis. Gastrointestinal Endoscopy 2014;79:233-241.e2.
432. Ell C, May A, Gossner L, et al. Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. Gastroenterology 2000;118:670-677.
433. Ell C, May A, Pech O, et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointestinal Endoscopy 2007;65:3-10.
434. Pech O, Behrens A, May A, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut 2008;57:1200-1206.
435. Chennat J, Konda VJA, Ross AS, et al. Complete Barrett's Eradication Endoscopic Mucosal Resection: An Effective Treatment Modality for High-Grade Dysplasia and Intramucosal Carcinoma-An American Single-Center Experience. The American Journal of Gastroenterology 2009;104:2684-2692.
436. Moss A, Bourke MJ, Hourigan LF, et al. Endoscopic Resection for Barrett's High-Grade Dysplasia and Early Esophageal Adenocarcinoma: An Essential Staging Procedure With Long-Term Therapeutic Benefit. American Journal of Gastroenterology 2010;105:1276-1283.
437. Pouw RE, Wirths K, Eisendrath P, et al. Efficacy of Radiofrequency Ablation Combined With Endoscopic Resection for Barrett's Esophagus With Early Neoplasia. Clinical Gastroenterology and Hepatology 2010;8:23-29.
438. van Vilsteren FGI, Pouw RE, Seewald S, et al. Stepwise radical endoscopic resection versus radiofrequency ablation for Barrett's esophagus with high-grade dysplasia or early cancer: a multicentre randomised trial. Gut 2011;60:765-773.
439. Manner H, May A, Pech O, et al. Early Barrett's Carcinoma With "Low-Risk" Submucosal Invasion: Long-Term Results of Endoscopic Resection With a Curative Intent. The American Journal of Gastroenterology 2008;103:2589-2597.
440. Manner H, Pech O, Heldmann Y, et al. Efficacy, Safety, and Long-term Results of Endoscopic Treatment for Early Stage Adenocarcinoma of the Esophagus With Low-risk sm1 Invasion. Clinical Gastroenterology and Hepatology 2013;11:630-635.
441. Alvarez Herrero L, Pouw R, van Vilsteren F, et al. Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: study based on endoscopic resection specimens. Endoscopy 2010;42:1030-1036.
442. Terheggen G, Horn EM, Vieth M, et al. A randomised trial of endoscopic submucosal dissection versus endoscopic mucosal resection for early Barrett's neoplasia. Gut 2016;66:783-793.
443. Qumseya BJ, Bartel MJ, Gendy S, et al. High rate of over-staging of Barrett's neoplasia with endoscopic ultrasound: systemic review and meta-analysis. Digestive and Liver Disease 2018;50:438-445.

444. Bartel MJ, Wallace TM, Gomez-Esquivel RD, et al. Role of EUS in patients with suspected Barrett's esophagus with high-grade dysplasia or early esophageal adenocarcinoma: impact on endoscopic therapy. Gastrointestinal Endoscopy 2017;86:292-298.
445. Qumseya BJ, Brown J, Abraham M, et al. Diagnostic performance of EUS in predicting advanced cancer among patients with Barrett's esophagus and high-grade dysplasia/early adenocarcinoma: systematic review and meta-analysis. Gastrointestinal Endoscopy 2015;81:865-874.e2.
446. Bergeron EJ, Lin J, Chang AC, et al. Endoscopic ultrasound is inadequate to determine which T1/T2 esophageal tumors are candidates for endoluminal therapies. The Journal of Thoracic and Cardiovascular Surgery 2014;147:765-773.
447. Wolfsen HC, Crook JE, Krishna M, et al. Prospective, Controlled Tandem Endoscopy Study of Narrow Band Imaging for Dysplasia Detection in Barrett's Esophagus. Gastroenterology 2008;135:24-31.
448. Behrens A, Pech O, Wuthnow E, et al. Detection of early neoplasia in Barrett's esophagus: a plea for the value of index endoscopy and 4-quadrant biopsies in short-segment Barrett's esophagus. Journal of Gastroenterology 2015;53:568-572.
449. Schölvinck D, van der Meulen K, Bergman J, et al. Detection of lesions in dysplastic Barrett's esophagus by community and expert endoscopists. Endoscopy 2016;49:113-120.
450. Bennett C, Vakil N, Bergman J, et al. Consensus Statements for Management of Barrett's Dysplasia and Early-Stage Esophageal Adenocarcinoma, Based on a Delphi Process. Gastroenterology 2012;143:336-346.
451. Pouw RE, Heldoorn N, Herrero LA, et al. Do we still need EUS in the workup of patients with early esophageal neoplasia? A retrospective analysis of 131 cases. Gastrointestinal Endoscopy 2011;73:662-668.
452. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. New England Journal of Medicine 2009;360:2277-2288.
453. Shaheen NJ, Overholt BF, Sampliner RE, et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology 2011;141:460-468.
454. Pouw RE, Seewald S, Gondrie JJ, et al. Stepwise radical endoscopic resection for eradication of Barrett's esophagus with early neoplasia in a cohort of 169 patients. Gut 2010;59:1169-1177.
455. Orman ES, Li N, Shaheen NJ. Efficacy and Durability of Radiofrequency Ablation for Barrett's Esophagus: Systematic Review and Meta-analysis. Clinical Gastroenterology and Hepatology 2013;11:1245-1255.
456. Manner H, May A, Kouti I, et al. Efficacy and safety of Hybrid-APC for the ablation of Barrett's esophagus. Surgical Endoscopy 2015;30:1364-1370.
457. Peerally MF, Bhandari P, Ragunath K, et al. Radiofrequency ablation compared with argon plasma coagulation after endoscopic resection of high-grade dysplasia or stage T1 adenocarcinoma in Barrett's esophagus: a randomized pilot study (BRIDE). Gastrointestinal Endoscopy 2019;89:680-689.
458. Alzoubaidi D, Hussein M, Sehgal V, et al. Cryoballoon ablation for treatment of patients with refractory esophageal neoplasia after first line endoscopic eradication therapy. Endoscopy International Open 2020;08:E891-E899.
459. Westerveld DR, Nguyen K, Banerjee D, et al. Safety and effectiveness of balloon cryoablation for treatment of Barrett's associated neoplasia: systematic review and meta-analysis. Endoscopy International Open 2020;08:E172-E178.
460. van Munster SN, Overwater A, Raicu MGM, et al. A novel cryoballoon ablation system for eradication of dysplastic Barrett's esophagus: a first-in-human feasibility study. Endoscopy 2020;52:193-201.
461. Nasr AO, Dillon MF, Conlon S, et al. Acid suppression increases rates of Barrett's esophagus and esophageal injury in the presence of duodenal reflux. Surgery 2012;151:382-390.
462. Desai M, Saligram S, Gupta N, et al. Efficacy and safety outcomes of multimodal endoscopic eradication therapy in Barrett's esophagus-related neoplasia: a systematic review and pooled analysis. Gastrointestinal Endoscopy 2017;85:482-495.e4.
463. Sawas T, Alsawas M, Bazerbachi F, et al. Persistent intestinal metaplasia after endoscopic eradication therapy of neoplastic Barrett's esophagus increases the risk of dysplasia recurrence: meta-analysis. Gastrointestinal Endoscopy 2019;89:913-925.e6.
464. Guthikonda A, Cotton CC, Madanick RD, et al. Clinical Outcomes Following Recurrence of Intestinal Metaplasia After Successful Treatment of Barrett's Esophagus With Radiofrequency Ablation. Am J Gastroenterol 2017;112:87-94.

465. Krishnamoorthi R, Singh S, Ragunathan K, et al. Risk of recurrence of Barrett's esophagus after successful endoscopic therapy. Gastrointestinal Endoscopy 2016;83:1090-1106.e3.
466. Cotton CC, Haidry R, Thrift AP, et al. Development of Evidence-Based Surveillance Intervals After Radiofrequency Ablation of Barrett's Esophagus. Gastroenterology 2018;155:316-326.e6.
467. Feith M, Stein HJ, Siewert JRd. Pattern of Lymphatic Spread of Barrett?s Cancer. World Journal of Surgery 2003;27:1052-1057.
468. Schölvinck D, Künzli H, Meijer S, et al. Management of patients with T1b esophageal adenocarcinoma: a retrospective cohort study on patient management and risk of metastatic disease. Surgical Endoscopy 2016;30:4102-4113.
469. Graham D, Sever N, Magee C, et al. Risk of lymph node metastases in patients with T1b oesophageal adenocarcinoma: A retrospective single centre experience. World Journal of Gastroenterology 2018;24:4698-4707.
470. Sawas T, Iyer PG, Alsawas M, et al. Higher Rate of Barrett's Detection in the First Year After Successful Endoscopic Therapy: Meta-analysis. American Journal of Gastroenterology 2018;113:959-971.
471. Cotton CC, Wolf WA, Pasricha S, et al. Recurrent intestinal metaplasia after radiofrequency ablation for Barrett's esophagus: endoscopic findings and anatomic location. Gastrointestinal Endoscopy 2015;81:1362-1369.
472. Fujii-Lau L, Cinnor B, Shaheen N, et al. Recurrence of intestinal metaplasia and early neoplasia after endoscopic eradication therapy for Barrett's esophagus: a systematic review and meta-analysis. Endoscopy International Open 2017;05:E430-E449.
473. Tan MC, Kanthasamy KA, Yeh AG, et al. Factors Associated With Recurrence of Barrett's Esophagus After Radiofrequency Ablation. Clinical Gastroenterology and Hepatology 2019;17:65-72.e5.
474. O'Byrne LM, Witherspoon J, Verhage RJJ, et al. Barrett's Registry Collaboration of academic centers in Ireland reveals high progression rate of low-grade dysplasia and low risk from nondysplastic Barrett's esophagus: report of the RIBBON network. Diseases of the Esophagus 2020;33.
475. Allen JE, Desai M, Roumans CAM, et al. Low risk of progression of Barrett's esophagus to neoplasia in women. Journal of Clinical Gastroenterology 2020;55:321-326.
476. Parasa S, Vennalaganti S, Gaddam S, et al. Development and Validation of a Model to Determine Risk of Progression of Barrett's Esophagus to Neoplasia. Gastroenterology 2018;154:1282-1289.e2.
477. van Sandick JW, van Lanschot JJB, Kuiken BW, et al. Impact of endoscopic biopsy surveillance of Barrett's oesophagus on pathological stage and clinical outcome of Barrett's carcinoma. Gut 1998;43:216-222.
478. Streitz JM, Andrews CW, Ellis FH. Endoscopic surveillance of Barrett's esophagus. The Journal of Thoracic and Cardiovascular Surgery 1993;105:383-388.
479. Fitzgerald RC, Saeed IT, Khoo D, et al. Rigorous surveillance protocol increases detection of curable cancers associated with Barrett's esophagus. Dig Dis Sci 2001;46:1892-8.
480. Wright TA, Gray MR, Morris AI, et al. Cost effectiveness of detecting Barrett's cancer. Gut 1996;39:574-579.
481. Corley DA, Levin TR, Habel LA, et al. Surveillance and survival in Barrett's adenocarcinomas: A population-based study. Gastroenterology 2002;122:633-640.
482. Streitz JM, Ellis HF, Tilden RL, et al. Endoscopic Surveillance of Barrett's Esophagus: A Cost-Effectiveness Comparison With Mammographic Surveillance for Breast Cancer. American Journal of Gastroenterology 1998;93:911-915.
483. Wright TA. High-grade dysplasia in Barrett's oesophagus. British Journal of Surgery 1997;84:760-766.
484. Weston AP, Sharma P, Topalovski M, et al. Long-term follow-up of Barrett's high-grade dysplasia. The American Journal of Gastroenterology 2000;95:1888-1893.
485. Schnell TG, Sontag SJ, Chejfec G, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. Gastroenterology 2001;120:1607-1619.
486. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology 2007;133:1342-63.
487. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128:3-20.e6; quiz 21-2.

488. Papadopoulou A, Koletzko S, Heuschkel R, et al. Management guidelines of eosinophilic esophagitis in childhood. J Pediatr Gastroenterol Nutr 2014;58:107-18.
489. Dellon ES, Gonsalves N, Hirano I, et al. ACG clinical guideline: Evidenced-based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol 2013;108:679-92; quiz 693.
490. Lucendo AJ, Molina-Infante J, Arias Á, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterology Journal 2017;5:335-358.
491. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. Gastroenterology 2018;155:1022-1033.e10.
492. Molina-Infante J, Bredenoord AJ, Cheng E, et al. Proton pump inhibitor-responsive esophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic esophagitis. Gut 2016;65:524-31.
493. Katzka DA. The complex relationship between eosinophilic esophagitis and gastroesophageal reflux disease. Dig Dis 2014;32:93-7.
494. van Rhijn BD, Weijenborg PW, Verheij J, et al. Proton pump inhibitors partially restore mucosal integrity in patients with proton pump inhibitor-responsive esophageal eosinophilia but not eosinophilic esophagitis. Clin Gastroenterol Hepatol 2014;12:1815-23.e2.
495. Krarup AL, Villadsen GE, Mejlgaard E, et al. Acid hypersensitivity in patients with eosinophilic esophagitis. Scand J Gastroenterol 2010;45:273-81.
496. van Rhijn BD, Oors JM, Smout AJ, et al. Prevalence of esophageal motility abnormalities increases with longer disease duration in adult patients with eosinophilic esophagitis. Neurogastroenterol Motil 2014;26:1349-55.
497. Cheng E, Souza RF, Spechler SJ. Eosinophilic esophagitis: interactions with gastroesophageal reflux disease. Gastroenterology clinics of North America 2014;43:243-256.
498. Attwood SE, Smyrk TC, Demeester TR, et al. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci 1993;38:109-16.
499. Straumann A, Spichtin HP, Bernoulli R, et al [Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings]. Schweiz Med Wochenschr 1994;124:1419-29.
500. Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. Gastroenterology 2018;154:319-332.e3.
501. Giriens B, Yan P, Safroneeva E, et al. Escalating incidence of eosinophilic esophagitis in Canton of Vaud, Switzerland, 1993-2013: a population-based study. Allergy 2015;70:1633-9.
502. Dellon ES, Erichsen R, Baron JA, et al. The increasing incidence and prevalence of eosinophilic oesophagitis outpaces changes in endoscopic and biopsy practice: national population-based estimates from Denmark. Aliment Pharmacol Ther 2015;41:662-70.
503. Warners MJ, de Rooij W, van Rhijn BD, et al. Incidence of eosinophilic esophagitis in the Netherlands continues to rise: 20-year results from a nationwide pathology database. Neurogastroenterol Motil 2018;30.
504. Navarro P, Arias Á, Arias-González L, et al. Systematic review with meta-analysis: the growing incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. Aliment Pharmacol Ther 2019;49:1116-1125.
505. Ronkainen J, Talley NJ, Aro P, et al. Prevalence of oesophageal eosinophils and eosinophilic oesophagitis in adults: the population-based Kalixanda study. Gut 2007;56:615-20.
506. Veerappan GR, Perry JL, Duncan TJ, et al. Prevalence of eosinophilic esophagitis in an adult population undergoing upper endoscopy: a prospective study. Clin Gastroenterol Hepatol 2009;7:420-6, 426.e1-2.
507. Sealock RJ, Kramer JR, Verstovsek G, et al. The prevalence of esophageal eosinophilia and eosinophilic esophagitis: a prospective study in unselected patients presenting to endoscopy. Aliment Pharmacol Ther 2013;37:825-32.
508. Prasad GA, Talley NJ, Romero Y, et al. Prevalence and predictive factors of eosinophilic esophagitis in patients presenting with dysphagia: a prospective study. Am J Gastroenterol 2007;102:2627-32.
509. Hiremath GS, Hameed F, Pacheco A, et al. Esophageal food impaction and eosinophilic esophagitis: A retrospective study, systematic review, and meta-analysis. Dig Dis Sci 2015;60:3181-93.

510. Sengupta N, Tapper EB, Corban C, et al. The clinical predictors of aetiology and complications among 173 patients presenting to the Emergency Department with esophageal food bolus impaction from 2004-2014. Aliment Pharmacol Ther 2015;42:91-8.
511. Heerasing N, Lee SY, Alexander S, et al. Prevalence of eosinophilic oesophagitis in adults presenting with oesophageal food bolus obstruction. World J Gastrointest Pharmacol Ther 2015;6:244-7.
512. Gretarsdottir HM, Jonasson JG, Björnsson ES. Etiology and management of esophageal food impaction: a population based study. Scand J Gastroenterol 2015;50:513-8.
513. Truskaite K, Dlugosz A. Prevalence of Eosinophilic Esophagitis and Lymphocytic Esophagitis in Adults with Esophageal Food Bolus Impaction. Gastroenterol Res Pract 2016;2016:9303858.
514. Ettyreddy AR, Sink JR, Georg MW, et al. Association between Eosinophilic Esophagitis and Esophageal Food Impaction in the Pediatric Population. Otolaryngol Head Neck Surg 2018;159:750-754.
515. Dellon ES, Jensen ET, Martin CF, et al. Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol 2014;12:589-96.e1.
516. Hill DA, Grundmeier RW, Ramos M, et al. Eosinophilic Esophagitis Is a Late Manifestation of the Allergic March. J Allergy Clin Immunol Pract 2018;6:1528-1533.
517. González-Cervera J, Arias Á, Redondo-González O, et al. Association between atopic manifestations and eosinophilic esophagitis: A systematic review and meta-analysis. Ann Allergy Asthma Immunol 2017;118:582-590.e2.
518. Simon D, Cianferoni A, Spergel JM, et al. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. Allergy 2016;71:611-20.
519. Kottyan LC, Parameswaran S, Weirauch MT, et al. The genetic etiology of eosinophilic esophagitis. J Allergy Clin Immunol 2020;145:9-15.
520. Sánchez-García S, Rodríguez Del Río P, Escudero C, et al. Possible eosinophilic esophagitis induced by milk oral immunotherapy. J Allergy Clin Immunol 2012;129:1155-7.
521. Miehlke S, Alpan O, Schröder S, et al. Induction of eosinophilic esophagitis by sublingual pollen immunotherapy. Case Rep Gastroenterol 2013;7:363-8.
522. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol 2014;113:624-9.
523. Bégin P, Chan ES, Kim H, et al. CSACI guidelines for the ethical, evidence-based and patient-oriented clinical practice of oral immunotherapy in IgE-mediated food allergy. Allergy, Asthma & Clinical Immunology 2020;16:20.
524. Alexander ES, Martin LJ, Collins MH, et al. Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis. J Allergy Clin Immunol 2014;134:1084-1092.e1.
525. Allen-Brady K, Firszt R, Fang JC, et al. Population-based familial aggregation of eosinophilic esophagitis suggests a genetic contribution. J Allergy Clin Immunol 2017;140:1138-1143.
526. Martin LJ, He H, Collins MH, et al. Eosinophilic esophagitis (EoE) genetic susceptibility is mediated by synergistic interactions between EoE-specific and general atopic disease loci. J Allergy Clin Immunol 2018;141:1690-1698.
527. Straumann A, Spichtin HP, Grize L, et al. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. Gastroenterology 2003;125:1660-9.
528. Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology 2013;145:1230-6.e1-2.
529. Warners MJ, Oude Nijhuis RAB, de Wijkerslooth LRH, et al. The natural course of eosinophilic esophagitis and long-term consequences of undiagnosed disease in a large cohort. Am J Gastroenterol 2018;113:836-844.
530. Dellon ES, Kim HP, Sperry SL, et al. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc 2014;79:577-85.e4.
531. Lipka S, Kumar A, Richter JE. Impact of Diagnostic Delay and Other Risk Factors on Eosinophilic Esophagitis Phenotype and Esophageal Diameter. J Clin Gastroenterol 2016;50:134-40.
532. Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2011;9:400-9.e1.

533. Dellon ES, Woosley JT, Arrington A, et al. Rapid Recurrence of Eosinophilic Esophagitis Activity After Successful Treatment in the Observation Phase of a Randomized, Double-Blind, Double-Dummy Trial. Clin Gastroenterol Hepatol 2020;18:1483-1492.e2.
534. Straumann A, Lucendo AJ, Miehlke S, et al. Budesonide Orodispersible Tablets Maintain Remission in a Randomized, Placebo-Controlled Trial of Patients With Eosinophilic Esophagitis. Gastroenterology 2020;159:1672-1685.e5.
535. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. J Pediatr Gastroenterol Nutr 2009;48:30-6.
536. DeBrosse CW, Franciosi JP, King EC, et al. Long-term outcomes in pediatric-onset esophageal eosinophilia. J Allergy Clin Immunol 2011;128:132-8.
537. Bohm M, Jacobs JW, Jr, Gupta A, et al. Most children with eosinophilic esophagitis have a favorable outcome as young adults. Dis Esophagus 2017;30:1-6.
538. Miehlke S. Clinical features of eosinophilic esophagitis in children and adults. Best Pract Res Clin Gastroenterol 2015;29:739-748.
539. Dellon ES, Gibbs WB, Fritchie KJ, et al. Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2009;7:1305-13; quiz 1261.
540. Croese J, Fairley SK, Masson JW, et al. Clinical and endoscopic features of eosinophilic esophagitis in adults. Gastrointest Endosc 2003;58:516-22.
541. Shaheen NJ, Mukkada V, Eichinger CS, et al. Natural history of eosinophilic esophagitis: a systematic review of epidemiology and disease course. Dis Esophagus 2018;31.
542. Muir AB, Brown-Whitehorn T, Godwin B, et al. Eosinophilic esophagitis: early diagnosis is the key. Clin Exp Gastroenterol 2019;12:391-399.
543. Alexander R, Alexander JA, Ravi K, et al. Measurement of Observed Eating Behaviors in Patients With Active and Inactive Eosinophilic Esophagitis. Clin Gastroenterol Hepatol 2019;17:2371-2373.
544. Biedermann L, Holbreich M, Atkins D, et al. Food-induced immediate response of the esophagus-A newly identified syndrome in patients with eosinophilic esophagitis. Allergy 2021;76:339-347.
545. Taft TH, Guadagnoli L, Edlynn E. Anxiety and depression in eosinophilic esophagitis: a scoping review and recommendations for future research. J Asthma Allergy 2019;12:389-399.
546. Klinnert MD, Silveira L, Harris R, et al. Health-related quality of life over time in children with eosinophilic esophagitis and their families. J Pediatr Gastroenterol Nutr 2014;59:308-16.
547. Harris RF, Menard-Katcher C, Atkins D, et al. Psychosocial dysfunction in children and adolescents with eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2013;57:500-5.
548. Lucendo AJ, Arias-González L, Molina-Infante J, et al. Determinant factors of quality of life in adult patients with eosinophilic esophagitis. United European Gastroenterol J 2018;6:38-45.
549. Mukkada V, Falk GW, Eichinger CS, et al. Health-Related Quality of Life and Costs Associated With Eosinophilic Esophagitis: A Systematic Review. Clin Gastroenterol Hepatol 2018;16:495-503.e8.
550. Leigh LY, Spergel JM. An in-depth characterization of a large cohort of adult patients with eosinophilic esophagitis. Ann Allergy Asthma Immunol 2019;122:65-72.e1.
551. Lucendo A, Sánchez-Cazalilla M, Molina-Infante J, et al. Transcultural adaptation and validation of the "Adult Eosinophilic Esophagitis Quality of Life Questionnaire" into Spanish. Revista espanola de enfermedades digestivas : organo oficial de la Sociedad Espanola de Patologia Digestiva 2014;106:386-394.
552. Chehade M, Jones SM, Pesek RD, et al. Phenotypic Characterization of Eosinophilic Esophagitis in a Large Multicenter Patient Population from the Consortium for Food Allergy Research. J Allergy Clin Immunol Pract 2018;6:1534-1544.e5.
553. Straumann A, Aceves SS, Blanchard C, et al. Pediatric and adult eosinophilic esophagitis: similarities and differences. Allergy 2012;67:477-90.
554. Straumann A, Rossi L, Simon HU, et al. Fragility of the esophageal mucosa: a pathognomonic endoscopic sign of primary eosinophilic esophagitis? Gastrointest Endosc 2003;57:407-12.
555. Moawad FJ, Robinson CL, Veerappan GR, et al. The tug sign: an endoscopic feature of eosinophilic esophagitis. Am J Gastroenterol 2013;108:1938-9.
556. Sgouros SN, Bergele C, Mantides A. Eosinophilic esophagitis in adults: a systematic review. Eur J Gastroenterol Hepatol 2006;18:211-7.
557. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. Clin Gastroenterol Hepatol 2005;3:1198-206.

558. Kim HP, Vance RB, Shaheen NJ, et al. The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. Clin Gastroenterol Hepatol 2012;10:988-96.e5.
559. Hirano I, Moy N, Heckman MG, et al. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut 2013;62:489-95.
560. Dellon ES, Cotton CC, Gebhart JH, et al. Accuracy of the Eosinophilic Esophagitis Endoscopic Reference Score in Diagnosis and Determining Response to Treatment. Clin Gastroenterol Hepatol 2016;14:31-9.
561. van Rhijn BD, Warners MJ, Curvers WL, et al. Evaluating the endoscopic reference score for eosinophilic esophagitis: moderate to substantial intra- and interobserver reliability. Endoscopy 2014;46:1049-55.
562. van Rhijn BD, Verheij J, Smout AJ, et al. The Endoscopic Reference Score shows modest accuracy to predict histologic remission in adult patients with eosinophilic esophagitis. Neurogastroenterol Motil 2016;28:1714-1722.
563. Wechsler JB, Bolton SM, Amsden K, et al. Eosinophilic Esophagitis Reference Score Accurately Identifies Disease Activity and Treatment Effects in Children. Clin Gastroenterol Hepatol 2018;16:1056-1063.
564. Rodríguez-Sánchez J, Barrio-Andrés J, Nantes Castillejo O, et al. The Endoscopic Reference Score shows modest accuracy to predict either clinical or histological activity in adult patients with eosinophilic esophagitis. Aliment Pharmacol Ther 2017;45:300-309.
565. Dellon ES, Katzka DA, Collins MH, et al. Safety and Efficacy of Budesonide Oral Suspension Maintenance Therapy in Patients With Eosinophilic Esophagitis. Clin Gastroenterol Hepatol 2019;17:666-673.e8.
566. Dellon ES, Woosley JT, Arrington A, et al. Efficacy of Budesonide vs Fluticasone for Initial Treatment of Eosinophilic Esophagitis in a Randomized Controlled Trial. Gastroenterology 2019;157:65-73.e5.
567. Lucendo AJ, Miehlke S, Schlag C, et al. Efficacy of Budesonide Orodispersible Tablets as Induction Therapy for Eosinophilic Esophagitis in a Randomized Placebo-Controlled Trial. Gastroenterology 2019;157:74-86.e15.
568. Hirano I, Safroneeva E, Roumet MC, et al. Randomised clinical trial: the safety and tolerability of fluticasone propionate orally disintegrating tablets versus placebo for eosinophilic oesophagitis. Alimentary Pharmacology & Therapeutics 2020;51:750-759.
569. Andreae DA, Hanna MG, Magid MS, et al. Swallowed Fluticasone Propionate Is an Effective Long-Term Maintenance Therapy for Children With Eosinophilic Esophagitis. Am J Gastroenterol 2016;111:1187-97.
570. Oliva S, Rossetti D, Papoff P, et al. A New Formulation of Oral Viscous Budesonide in Treating Paediatric Eosinophilic Oesophagitis: A Pilot Study. J Pediatr Gastroenterol Nutr 2017;64:218-224.
571. Oliva S, Rossetti D, Papoff P, et al. A 12-Week Maintenance Therapy with a New Prepared Viscous Budesonide in Pediatric Eosinophilic Esophagitis. Dig Dis Sci 2019;64:1571-1578.
572. Reed CC, Fan C, Koutlas NT, et al. Food elimination diets are effective for long-term treatment of adults with eosinophilic esophagitis. Aliment Pharmacol Ther 2017;46:836-844.
573. Molina-Infante J, Arias Á, Alcedo J, et al. Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: The 2-4-6 study. J Allergy Clin Immunol 2018;141:1365-1372.
574. Hirano I, Collins MH, Assouline-Dayan Y, et al. RPC4046, a Monoclonal Antibody Against IL13, Reduces Histologic and Endoscopic Activity in Patients With Eosinophilic Esophagitis. Gastroenterology 2019;156:592-603.e10.
575. Hirano I, Dellon ES, Hamilton JD, et al. Efficacy of Dupilumab in a Phase 2 Randomized Trial of Adults With Active Eosinophilic Esophagitis. Gastroenterology 2020;158:111-122.e10.
576. Schoepfer AM, Hirano I, Coslovsky M, et al. Variation in Endoscopic Activity Assessment and Endoscopy Score Validation in Adults With Eosinophilic Esophagitis. Clin Gastroenterol Hepatol 2019;17:1477-1488.e10.
577. Gonsalves N, Policarpio-Nicolas M, Zhang Q, et al. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. Gastrointest Endosc 2006;64:313-9.
578. Shah A, Kagalwalla AF, Gonsalves N, et al. Histopathologic variability in children with eosinophilic esophagitis. Am J Gastroenterol 2009;104:716-21.

579. Peery AF, Cao H, Dominik R, et al. Variable reliability of endoscopic findings with white-light and narrow-band imaging for patients with suspected eosinophilic esophagitis. Clin Gastroenterol Hepatol 2011;9:475-80.
580. Dellon ES, Speck OW, K;, Woosley JT, et al. Su1129 The Patchy Nature of Esophageal Eosinophilia in Eosinophilic Esophagitis: Insights From Pathology Samples From a Clinical Trial. Gastroenterology 2012;142:S-432.
581. Saffari H, Peterson KA, Fang JC, et al. Patchy eosinophil distributions in an esophagectomy specimen from a patient with eosinophilic esophagitis: implications for endoscopic biopsy. J Allergy Clin Immunol 2012;130:798-800.
582. Salek J, Clayton F, Vinson L, et al. Endoscopic appearance and location dictate diagnostic yield of biopsies in eosinophilic esophagitis. Aliment Pharmacol Ther 2015;41:1288-95.
583. Nielsen JA, Lager DJ, Lewin M, et al. The optimal number of biopsy fragments to establish a morphologic diagnosis of eosinophilic esophagitis. Am J Gastroenterol 2014;109:515-20.
584. Krarup AL, Drewes AM, Ejstrud P, et al. Implementation of a biopsy protocol to improve detection of esophageal eosinophilia: a Danish registry-based study. Endoscopy 2021;53:15-24.
585. Lim JR, Gupta SK, Croffie JM, et al. White specks in the esophageal mucosa: An endoscopic manifestation of non-reflux eosinophilic esophagitis in children. Gastrointest Endosc 2004;59:835-8.
586. Gupta SK, Fitzgerald JF, Chong SK, et al. Vertical lines in distal esophageal mucosa (VLEM): a true endoscopic manifestation of esophagitis in children? Gastrointest Endosc 1997;45:485-9.
587. Kaur S, Rosen JM, Kriegermeier AA, et al. Utility of Gastric and Duodenal Biopsies During Follow-up Endoscopy in Children With Eosinophilic Esophagitis. J Pediatr Gastroenterol Nutr 2017;65:399-403.
588. Dellon ES, Speck O, Woodward K, et al. Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy: a prospective cohort study. Am J Gastroenterol 2013;108:1854-60.
589. de Rooij WE, Haasnoot ML, Lei A, et al. Utility of gastric and duodenal biopsy sampling in adult eosinophilic esophagitis patients to rule out other gastrointestinal disorders. Scand J Gastroenterol 2021;56:613-620.
590. Dellon ES, Aderoju A, Woosley JT, et al. Variability in diagnostic criteria for eosinophilic esophagitis: a systematic review. Am J Gastroenterol 2007;102:2300-13.
591. Peery AF, Shaheen NJ, Dellon ES. Practice patterns for the evaluation and treatment of eosinophilic oesophagitis. Aliment Pharmacol Ther 2010;32:1373-82.
592. Sperry SL, Shaheen NJ, Dellon ES. Toward uniformity in the diagnosis of eosinophilic esophagitis (EoE): the effect of guidelines on variability of diagnostic criteria for EoE. Am J Gastroenterol 2011;106:824-32; quiz 833.
593. Mueller S, Neureiter D, Aigner T, et al. Comparison of histological parameters for the diagnosis of eosinophilic esophagitis versus gastroesophageal reflux disease on esophageal biopsy material. Histopathology 2008;53:676-84.
594. Dellon ES, Speck O, Woodward K, et al. Distribution and variability of esophageal eosinophilia in patients undergoing upper endoscopy. Mod Pathol 2015;28:383-90.
595. Collins MH. Histopathologic features of eosinophilic esophagitis and eosinophilic gastrointestinal diseases. Gastroenterol Clin North Am 2014;43:257-68.
596. Collins MH, Martin LJ, Alexander ES, et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. Dis Esophagus 2017;30:1-8.
597. Warners MJ, Hindryckx P, Levesque BG, et al. Systematic Review: Disease Activity Indices in Eosinophilic Esophagitis. Am J Gastroenterol 2017;112:1658-1669.
598. Hirano I, Collins MH, Katzka DA, et al. Budesonide Oral Suspension Improves Outcomes in Patients With Eosinophilic Esophagitis: Results from a Phase 3 Trial. Clinical Gastroenterology and Hepatology 2021;20:525-534.e10.
599. Konikoff MR, Blanchard C, Kirby C, et al. Potential of blood eosinophils, eosinophil-derived neurotoxin, and eotaxin-3 as biomarkers of eosinophilic esophagitis. Clin Gastroenterol Hepatol 2006;4:1328-36.
600. Straumann A, Conus S, Degen L, et al. Budesonide Is Effective in Adolescent and Adult Patients With Active Eosinophilic Esophagitis. Gastroenterology 2010;139:1526-1537.e1.

601. Rodríguez-Sánchez J, Gómez-Torrijos E, de-la-Santa-Belda E, et al. Effectiveness of serological markers of eosinophil activity in monitoring eosinophilic esophagitis. Rev Esp Enferm Dig 2013;105:462-7.
602. Schlag C, Miehlke S, Heiseke A, et al. Peripheral blood eosinophils and other non-invasive biomarkers can monitor treatment response in eosinophilic esophagitis. Aliment Pharmacol Ther 2015;42:1122-30.
603. Min SB, Nylund CM, Baker TP, et al. Longitudinal Evaluation of Noninvasive Biomarkers for Eosinophilic Esophagitis. J Clin Gastroenterol 2017;51:127-135.
604. Rao GS, Mitchell L, Ohnuki L, et al. Can Eosinophil Derived Neurotoxin (EDN) Act As a Surrogate Marker of Disease Activity in Children with Allergic Eosinophilic Esophagitis (AEE)? Gastrointestinal Endoscopy 2004;59:P103.
605. Leung J, Nguyen-Traxler A, Lee EM, et al. Assessment of fractionated exhaled nitric oxide as a biomarker for the treatment of eosinophilic esophagitis. Allergy and asthma proceedings 2012;33:519-524.
606. Dellon ES, Rusin S, Gebhart JH, et al. Utility of a Noninvasive Serum Biomarker Panel for Diagnosis and Monitoring of Eosinophilic Esophagitis: A Prospective Study. Am J Gastroenterol 2015;110:821-7.
607. Hines BT, Rank MA, Wright BL, et al. Minimally invasive biomarker studies in eosinophilic esophagitis: A systematic review. Ann Allergy Asthma Immunol 2018;121:218-228.
608. Furuta GT, Kagalwalla AF, Lee JJ, et al. The esophageal string test: a novel, minimally invasive method measures mucosal inflammation in eosinophilic esophagitis. Gut 2013;62:1395-405.
609. Katzka DA, Geno DM, Ravi A, et al. Accuracy, safety, and tolerability of tissue collection by Cytosponge vs endoscopy for evaluation of eosinophilic esophagitis. Clin Gastroenterol Hepatol 2015;13:77-83.e2.
610. Gonsalves N, Yang GY, Doerfler B, et al. Elimination Diet Effectively Treats Eosinophilic Esophagitis in Adults; Food Reintroduction Identifies Causative Factors. Gastroenterology 2012;142:1451-1459.e1.
611. Lucendo AJ, Arias Á, González-Cervera J, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: A prospective study on the food cause of the disease. Journal of Allergy and Clinical Immunology 2013;131:797-804.
612. Eckmann JD, Ravi K, Katzka DA, et al. Efficacy of Atopy Patch Testing in Directed Dietary Therapy of Eosinophilic Esophagitis: A Pilot Study. Dig Dis Sci 2018;63:694-702.
613. Philpott H, Nandurkar S, Royce SG, et al. Allergy tests do not predict food triggers in adult patients with eosinophilic esophagitis. A comprehensive prospective study using five modalities. Aliment Pharmacol Ther 2016;44:223-33.
614. Hirano I, Chan ES, Rank MA, et al. AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis. Gastroenterology 2020;158:1776-1786.
615. Straumann A, Katzka DA. Diagnosis and Treatment of Eosinophilic Esophagitis. Gastroenterology 2018;154:346-359.
616. Konikoff MR, Noel RJ, Blanchard C, et al. A Randomized, Double-Blind, Placebo-Controlled Trial of Fluticasone Propionate for Pediatric Eosinophilic Esophagitis. Gastroenterology 2006;131:1381-1391.
617. Dohil R, Newbury R, Fox L, et al. Oral Viscous Budesonide Is Effective in Children With Eosinophilic Esophagitis in a Randomized, Placebo-Controlled Trial. Gastroenterology 2010;139:418-429.e1.
618. Alexander JA, Jung KW, Arora AS, et al. Swallowed Fluticasone Improves Histologic but Not Symptomatic Response of Adults With Eosinophilic Esophagitis. Clinical Gastroenterology and Hepatology 2012;10:742-749.e1.
619. Butz BK, Wen T, Gleich GJ, et al. Efficacy, Dose Reduction, and Resistance to High-Dose Fluticasone in Patients With Eosinophilic Esophagitis. Gastroenterology 2014;147:324-333.e5.
620. Gupta SK, Vitanza JM, Collins MH. Efficacy and Safety of Oral Budesonide Suspension in Pediatric Patients With Eosinophilic Esophagitis. Clinical Gastroenterology and Hepatology 2015;13:66-76.e3.
621. Miehlke S, Hruz P, Vieth M, et al. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. Gut 2015;65:390-399.

622. Dellon ES, Katzka DA, Collins MH, et al. Budesonide Oral Suspension Improves Symptomatic, Endoscopic, and Histologic Parameters Compared With Placebo in Patients With Eosinophilic Esophagitis. Gastroenterology 2017;152:776-786.e5.
623. Schaefer ET, Fitzgerald JF, Molleston JP, et al. Comparison of Oral Prednisone and Topical Fluticasone in the Treatment of Eosinophilic Esophagitis: A Randomized Trial in Children. Clinical Gastroenterology and Hepatology 2008;6:165-173.
624. Peterson KA, Thomas KL, Hilden K, et al. Comparison of Esomeprazole to Aerosolized, Swallowed Fluticasone for Eosinophilic Esophagitis. Digestive Diseases and Sciences 2010;55:1313-1319.
625. Moawad FJ, Veerappan GR, Dias JA, et al. Randomized Controlled Trial Comparing Aerosolized Swallowed Fluticasone to Esomeprazole for Esophageal Eosinophilia. American Journal of Gastroenterology 2013;108:366-372.
626. Dellon ES, Sheikh A, Speck O, et al. Viscous Topical Is More Effective Than Nebulized Steroid Therapy for Patients With Eosinophilic Esophagitis. Gastroenterology 2012;143:321-324.e1.
627. Chuang M-y, Chinnaratha MA, Hancock DG, et al. Topical Steroid Therapy for the Treatment of Eosinophilic Esophagitis (EoE): A Systematic Review and Meta-Analysis. Clinical and Translational Gastroenterology 2015;6:e82.
628. Tan ND, Xiao YL, Chen MH. Steroids therapy for eosinophilic esophagitis: systematic review and meta-analysis. Journal of Digestive Diseases 2015;16:431-442.
629. Lipka S, Kumar A, Miladinovic B, et al. Systematic review with network meta-analysis: comparative effectiveness of topical steroids vs. PPIs for the treatment of the spectrum of eosinophilic oesophagitis. Alimentary Pharmacology & Therapeutics 2016;43:663-673.
630. Murali AR, Gupta A, Attar BM, et al. Topical steroids in eosinophilic esophagitis: Systematic review and meta-analysis of placebo-controlled randomized clinical trials. Journal of Gastroenterology and Hepatology 2016;31:1111-1119.
631. Rokkas T, Niv Y, Malfertheiner P. A Network Meta-Analysis of Randomized Controlled Trials on the Treatment of Eosinophilic Esophagitis in Adults and Children. Journal of Clinical Gastroenterology 2020;55:400-410.
632. de Heer J, Miehlke S, Rösch T, et al. Histologic and Clinical Effects of Different Topical Corticosteroids for Eosinophilic Esophagitis: Lessons from an Updated Meta-Analysis of Placebo-Controlled Randomized Trials. Digestion 2020;102:377-385.
633. Miehlke S, Lucendo AJ, Straumann A, et al. Orodispersible budesonide tablets for the treatment of eosinophilic esophagitis: a review of the latest evidence. Therapeutic Advances in Gastroenterology 2020;13:175628482092728.
634. Miehlke S, Schlag C, Lucendo AJ, et al. Budesonide orodispersible tablets for induction of remission in patients with active eosinophilic oesophagitis: A 6-week open-label trial of the EOS-2 Programme. United European Gastroenterol J 2022;10:330-343.
635. Schlag C, Miehlke S, Lucendo A, et al. Mo1129 - Efficacy of Budesonide Orodispersible Tablets for Induction of Remission in Patients with Active Eosinophilic Esophagitis: Results from the 6-Week Open-Label Treatment Phase of Eos-2 Trial. Gastroenterology 2019;156:S-715.
636. Lucendo AJ, Arias Á, Molina-Infante J. Efficacy of Proton Pump Inhibitor Drugs for Inducing Clinical and Histologic Remission in Patients With Symptomatic Esophageal Eosinophilia: A Systematic Review and Meta-Analysis. Clinical Gastroenterology and Hepatology 2016;14:13-22.e1.
637. Gómez-Torrijos E, García-Rodríguez R, Castro-Jiménez A, et al. The efficacy of step-down therapy in adult patients with proton pump inhibitor-responsive esophageal eosinophilia. Alimentary Pharmacology and Therapeutics 2016;43:534-540.
638. Laserna-Mendieta EJ, Casabona S, Guagnozzi D, et al. Efficacy of proton pump inhibitor therapy for eosinophilic esophagitis in 630 patients: results from the EoE connect registry. Alimentary Pharmacology & Therapeutics 2020;52:798-807.
639. Alexander R, Alexander JA, Akambase J, et al. Proton pump inhibitor therapy in eosinophilic esophagitis: predictors of nonresponse. Digestive Diseases and Sciences 2020;66:3096-3104.
640. Kagalwalla AF, Shah A, Li BUK, et al. Identification of Specific Foods Responsible for Inflammation in Children With Eosinophilic Esophagitis Successfully Treated With Empiric Elimination Diet. Journal of Pediatric Gastroenterology & Nutrition 2011;53:145-149.
641. Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of Six-Food Elimination Diet on Clinical and Histologic Outcomes in Eosinophilic Esophagitis. Clinical Gastroenterology and Hepatology 2006;4:1097-1102.

642. Arias Á, González-Cervera J, Tenias JM, et al. Efficacy of Dietary Interventions for Inducing Histologic Remission in Patients With Eosinophilic Esophagitis: A Systematic Review and Meta-analysis. Gastroenterology 2014;146:1639-1648.
643. Groetch M, Venter C, Skypala I, et al. Dietary Therapy and Nutrition Management of Eosinophilic Esophagitis: A Work Group Report of the American Academy of Allergy, Asthma, and Immunology. The Journal of Allergy and Clinical Immunology: In Practice 2017;5:312-324.e29.
644. Kuchen T, Straumann A, Safroneeva E, et al. Swallowed topical corticosteroids reduce the risk for long-lasting bolus impactions in eosinophilic esophagitis. Allergy 2014;69:1248-54.
645. Greuter T, Safroneeva E, Bussmann C, et al. Maintenance Treatment Of Eosinophilic Esophagitis With Swallowed Topical Steroids Alters Disease Course Over A 5-Year Follow-up Period In Adult Patients. Clin Gastroenterol Hepatol 2019;17:419-428.e6.
646. Greuter T, Godat A, Ringel A, et al. Effectiveness and Safety of High- vs Low-Dose Swallowed Topical Steroids for Maintenance Treatment of Eosinophilic Esophagitis: A Multicenter Observational Study. Clin Gastroenterol Hepatol 2021;19:2514-2523.e2.
647. Molina-Infante J, Rodriguez-Sanchez J, Martinek J, et al. Long-Term Loss of Response in Proton Pump Inhibitor-Responsive Esophageal Eosinophilia Is Uncommon and Influenced by CYP2C19 Genotype and Rhinoconjunctivitis. Am J Gastroenterol 2015;110:1567-75.
648. Remedios M, Campbell C, Jones DM, et al. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. Gastrointest Endosc 2006;63:3-12.
649. Safroneeva E, Straumann A, Coslovsky M, et al. Symptoms Have Modest Accuracy in Detecting Endoscopic and Histologic Remission in Adults With Eosinophilic Esophagitis. Gastroenterology 2016;150:581-590.e4.
650 Safroneeva E, Schoepfer AM. Symptom-based patient-reported outcomes in adults with eosinophilic esophagitis: value for treatment monitoring and randomized controlled trial design. Curr Opin Allergy Clin Immunol 2019;19:169-174.
651. Schoepfer AM, Straumann A, Panczak R, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. Gastroenterology 2014;147:1255-66.e21.
652. Dellon ES, Irani AM, Hill MR, et al. Development and field testing of a novel patient-reported outcome measure of dysphagia in patients with eosinophilic esophagitis. Aliment Pharmacol Ther 2013;38:634-42.
653. Martin LJ, Franciosi JP, Collins MH, et al. Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease. J Allergy Clin Immunol 2015;135:1519-28.e8.
654. Taft TH, Kern E, Kwiatek MA, et al. The adult eosinophilic esophagitis quality of life questionnaire: a new measure of health-related quality of life. Aliment Pharmacol Ther 2011;34:790-8.
655. Franciosi JP, Hommel KA, Bendo CB, et al. PedsQL eosinophilic esophagitis module: feasibility, reliability, and validity. J Pediatr Gastroenterol Nutr 2013;57:57-66.
656. Kwiatek MA, Hirano I, Kahrilas PJ, et al. Mechanical properties of the esophagus in eosinophilic esophagitis. Gastroenterology 2011;140:82-90.
657. Menard-Katcher C, Benitez AJ, Pan Z, et al. Influence of Age and Eosinophilic Esophagitis on Esophageal Distensibility in a Pediatric Cohort. Am J Gastroenterol 2017;112:1466-1473.
658. Nicodème F, Hirano I, Chen J, et al. Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2013;11:1101-1107.e1.
659. Miehlke S, Schlag C, Storr M, et al [Eosinophilic esophagitis update: New Guidelines of the European Study Group EUREOS]. Z Gastroenterol 2018;56:139-150.
660. Schlag C, Dellon ES, Lucendo AJ, et al. Efficacy and safety of long-term therapy of eosinophilic esophagitis with a new oral dissolving fluticasone tablet (APT-1011): Results of an international randomized double-blind placebo-controlled phase 2b study. Z Gastroenterol 2020;58:e129.
661. Greuter T, Bussmann C, Safroneeva E, et al. Long-Term Treatment of Eosinophilic Esophagitis With Swallowed Topical Corticosteroids: Development and Evaluation of a Therapeutic Concept. Am J Gastroenterol 2017;112:1527-1535.
662. Gutiérrez-Junquera C, Fernández-Fernández S, Cilleruelo ML, et al. High Prevalence of Response to Proton-pump Inhibitor Treatment in Children With Esophageal Eosinophilia. J Pediatr Gastroenterol Nutr 2016;62:704-10.

663. Kagalwalla AF, Wechsler JB, Amsden K, et al. Efficacy of a 4-Food Elimination Diet for Children With Eosinophilic Esophagitis. Clin Gastroenterol Hepatol 2017;15:1698-1707.e7.
664. Kagalwalla AF, Amsden K, Shah A, et al. Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2012;55:711-6.
665. Wechsler JB, Schwartz S, Arva NC, et al. A Single Food Milk Elimination Diet Is Effective for Treatment of Eosinophilic Esophagitis in Children. Clin Gastroenterol Hepatol 2021.
666. Chehade M, Sher E. Medical therapy versus dietary avoidance in eosinophilic esophagitis: which approach is better? Allergy Asthma Proc 2017;38:170-176.
667. Molina-Infante J, Martin-Noguerol E, Alvarado-Arenas M, et al. Selective elimination diet based on skin testing has suboptimal efficacy for adult eosinophilic esophagitis. J Allergy Clin Immunol 2012;130:1200-2.
668. Wolf WA, Jerath MR, Sperry SL, et al. Dietary elimination therapy is an effective option for adults with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2014;12:1272-9.
669. Markowitz JE, Spergel JM, Ruchelli E, et al. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol 2003;98:777-82.
670 Spergel JM. Eosinophilic esophagitis in adults and children: evidence for a food allergy component in many patients. Curr Opin Allergy Clin Immunol 2007;7:274-8.
671. Henderson CJ, Abonia JP, King EC, et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. J Allergy Clin Immunol 2012;129:1570-8.
672. Peterson KA, Byrne KR, Vinson LA, et al. Elemental diet induces histologic response in adult eosinophilic esophagitis. Am J Gastroenterol 2013;108:759-66.
673. Straumann A, Bussmann C, Zuber M, et al. Eosinophilic esophagitis: analysis of food impaction and perforation in 251 adolescent and adult patients. Clin Gastroenterol Hepatol 2008;6:598-600.
674. Schoepfer AM, Gonsalves N, Bussmann C, et al. Esophageal dilation in eosinophilic esophagitis: effectiveness, safety, and impact on the underlying inflammation. Am J Gastroenterol 2010;105:1062-70.
675. Moawad FJ, Cheatham JG, DeZee KJ. Meta-analysis: the safety and efficacy of dilation in eosinophilic esophagitis. Aliment Pharmacol Ther 2013;38:713-20.
676. Jacobs JW, Jr, Spechler SJ. A systematic review of the risk of perforation during esophageal dilation for patients with eosinophilic esophagitis. Dig Dis Sci 2010;55:1512-5.
677. Dougherty M, Runge TM, Eluri S, et al. Esophageal dilation with either bougie or balloon technique as a treatment for eosinophilic esophagitis: a systematic review and meta-analysis. Gastrointest Endosc 2017;86:581-591.e3.
678. Jung KW, Gundersen N, Kopacova J, et al. Occurrence of and risk factors for complications after endoscopic dilation in eosinophilic esophagitis. Gastrointest Endosc 2011;73:15-21.
679. Netzer P, Gschossmann JM, Straumann A, et al. Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission. Eur J Gastroenterol Hepatol 2007;19:865-9.
680. Abonia JP, Blanchard C, Butz BB, et al. Involvement of mast cells in eosinophilic esophagitis. J Allergy Clin Immunol 2010;126:140-9.
681. Attwood SE, Lewis CJ, Bronder CS, et al. Eosinophilic oesophagitis: a novel treatment using montelukast. Gut 2003;52:181-5.
682. Stumphy J, Al-Zubeidi D, Guerin L, et al. Observations on use of montelukast in pediatric eosinophilic esophagitis: insights for the future. Dis Esophagus 2011;24:229-34.
683. Lucendo AJ, De Rezende LC, Jiménez-Contreras S, et al. Montelukast was inefficient in maintaining steroid-induced remission in adult eosinophilic esophagitis. Dig Dis Sci 2011;56:3551-8.
684. Straumann A, Hoesli S, Bussmann C, et al. Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. Allergy 2013;68:375-85.
685. de Rooij WE, Dellon ES, Parker CE, et al. Pharmacotherapies for the Treatment of Eosinophilic Esophagitis: State of the Art Review. Drugs 2019;79:1419-1434.
686. Blanchard C, Stucke EM, Rodriguez-Jimenez B, et al. A striking local esophageal cytokine expression profile in eosinophilic esophagitis. J Allergy Clin Immunol 2011;127:208-17, 217.e1-7.
687. Blanchard C, Mingler MK, Vicario M, et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. J Allergy Clin Immunol 2007;120:1292-300.

688. Dellon ES, Rothenberg ME, Collins MH, et al. Dupilumab Efficacy and Safety in Adult and Adolescent Patients with Eosinophilic Esophagitis: Results from Part A of a Randomized, Placebo-Controlled Three-Part, Phase 3 Study (Abstract). United European Gastroenterology Journal 2020;8:1258-1275.
689. Dellon ES, Collins MH, Rothenberg ME, et al. Long-term Efficacy and Tolerability of RPC4046 in an Open-Label Extension Trial of Patients With Eosinophilic Esophagitis. Clin Gastroenterol Hepatol 2021;19:473-483.e17.
690. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. Gut 2010;59:21-30.
691. Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterology 2011;141:1593-604.
692. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol 2012;129:456-63, 463.e1-3.
693. Clayton F, Fang JC, Gleich GJ, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. Gastroenterology 2014;147:602-9.
694. Rothenberg ME, Wen T, Greenberg A, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. J Allergy Clin Immunol 2015;135:500-7.
695. Straumann A, Bussmann C, Conus S, et al. Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. J Allergy Clin Immunol 2008;122:425-7.
696. Molina-Infante J, Gonzalez-Cordero PL, Arias A, et al. Update on dietary therapy for eosinophilic esophagitis in children and adults. Expert Rev Gastroenterol Hepatol 2017;11:115-123.
697. Gutiérrez-Junquera C, Fernández-Fernández S, Cilleruelo ML, et al. The Role of Proton Pump Inhibitors in the Management of Pediatric Eosinophilic Esophagitis. Frontiers in Pediatrics 2018;6.
698. Zhang X, Cheng E, Huo X, et al. Omeprazole Blocks STAT6 Binding to the Eotaxin-3 Promoter in Eosinophilic Esophagitis Cells. PLOS ONE 2012;7:e50037.
699. Cheng E, Zhang X, Huo X, et al. Omeprazole blocks eotaxin-3 expression by esophageal squamous cells from patients with eosinophilic esophagitis and GORD. Gut 2013;62:824-32.
700. Park JY, Zhang X, Nguyen N, et al. Proton pump inhibitors decrease eotaxin-3 expression in the proximal esophagus of children with esophageal eosinophilia. PLoS One 2014;9:e101391.
701. Shoda T, Matsuda A, Nomura I, et al. Eosinophilic esophagitis versus proton pump inhibitor-responsive esophageal eosinophilia: transcriptome analysis. J Allergy Clin Immunol 2017;139:2010-2013.e4.
702. Wen T, Dellon ES, Moawad FJ, et al. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. J Allergy Clin Immunol 2015;135:187-97.
703. Cañas JA, Tabares A, Barbero C, et al. Proton-pump Inhibitor Response Prediction Using Esophageal microRNAs in Children With Eosinophilic Esophagitis. J Pediatr Gastroenterol Nutr 2020;71:755-763.
704. Aceves SS, Bastian JF, Newbury RO, et al. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. Am J Gastroenterol 2007;102:2271-9; quiz 2280.
705. Golekoh MC, Hornung LN, Mukkada VA, et al. Adrenal insufficiency after chronic swallowed glucocorticoid therapy for eosinophilic esophagitis. J Pediatr 2016;170:240-5.
706. Ahmet A, Benchimol EI, Goldbloom EB, et al. Adrenal suppression in children treated with swallowed fluticasone and oral viscous budesonide for eosinophilic esophagitis. Allergy Asthma Clin Immunol 2016;12:49.
707. Axelsson I, Naumburg E, Prietsch SO, et al. Inhaled corticosteroids in children with persistent asthma: effects of different drugs and delivery devices on growth. Cochrane Database Syst Rev 2019;6:Cd010126.
708. Cianferoni A, Spergel J. Eosinophilic esophagitis: A Comprehensive Review. Clin Rev Allergy Immunol 2016;50:159-74.
709. Bolton SM, Kagalwalla AF, Wechsler JB. Eosinophilic esophagitis in children: endoscopic findings at diagnosis and post-intervention. Curr Gastroenterol Rep 2018;20:4.
710. Ferreira CT, Vieira MC, Furuta GT, et al. Eosinophilic esophagitis-Where are we today? J Pediatr (Rio J) 2019;95:275-281.

711. Aceves SS, Newbury RO, Chen D, et al. Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. Allergy 2010;65:109-16.
712. Runge TM, Eluri S, Woosley JT, et al. Control of inflammation decreases the need for subsequent esophageal dilation in patients with eosinophilic esophagitis. Dis Esophagus 2017;30:1-7.
713. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol 2012;130:461-7.e5.
714. Simon D, Straumann A, Simon HU. Eosinophilic esophagitis and allergy. Dig Dis 2014;32:30-3.
715. Mishra A, Hogan SP, Brandt EB, et al. An etiological role for aeroallergens and eosinophils in experimental esophagitis. The Journal of clinical investigation 2001;107:83-90.
716. Cianferoni A, Shuker M, Brown-Whitehorn T, et al. Food avoidance strategies in eosinophilic oesophagitis. Clin Exp Allergy 2019;49:269-284.
717. Gonsalves N. Eosinophilic gastrointestinal disorders. Clin Rev Allergy Immunol 2019;57:272-285.
718. Molina-Infante J, Arias A, Barrio J, et al. Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study. J Allergy Clin Immunol 2014;134:1093-9.e1.
719. Furuta GT, Katzka DA. Eosinophilic esophagitis. N Engl J Med 2015;373:1640-8.
720. Du Toit G, Sayre PH, Roberts G, et al. Effect of Avoidance on Peanut Allergy after Early Peanut Consumption. N Engl J Med 2016;374:1435-43.

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