Moving forward: new insights into esophageal motility disorders

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Moving forward: new insights into esophageal motility disorders

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PART I – GASTROESOPHAGEAL REFLUX DISEASE

1

p. 8

General introduction and thesis outline

2

p. 24

Utility of routine esophageal biopsies in patients with refractory reflux symptoms

American Journal of Gastroenterology, 2021

3

p. 40

Characterization of patients with nighttime reflux symptoms: observations made with prolonged wireless esophageal pH monitoring

Alimentary Pharmacology & Therapeutics, 2021

PART II – ACHALASIA

6

p. 106

European guidelines on achalasia: United European Gastroenterology and European Society of Neurogastroenterology and Motility recommendations

United European Gastroenterology Journal, 2020

7

p. 150

Factors associated with achalasia treatment outcomes: systematic review and meta-analysis

Clinical Gastroenterology and Hepatology, 2020

8

p. 180

Non-surgical treatment of esophageal perforation after pneumatic dilation for achalasia: a case series

Scandinavian Journal of Gastroenterology, 2020

4

p. 60

The effect of STW5 (Iberogast) on reflux symptoms in dyspeptic patients: a double-blind randomized placebo-controlled crossover trial

Submitted

5

p. 80

The natural course of giant paraesophageal hernia and long-term outcomes following conservative management

United European Gastroenterology Journal, 2020

PART III – INABILITY TO BELCH SYNDROME

9

p. 192

The inability to belch syndrome: a study using concurrent high-resolution manometry and impedance monitoring

Neurogastroenterology & Motility, 2021

10

p. 212

Summary
Discussion and future perspectives

&

p. 230

Samenvatting (NL)
Contributing authors
List of publications
PhD portfolio
About the author
Dankwoord

1

General introduction and thesis outline

INTRODUCTION

The esophagus

The esophagus is a muscular tube that facilitates food bolus passage from the pharynx to the stomach and consists of multiple layers (Figure 1). The inner layer, or mucosa, forms the barrier between the luminal content and the internal environment. It is encircled by the submucosal plexus, a tangled network of nerve fibers involved in pain perception, absorption and mucus secretion.[1] The mucosa and submucosa are surrounded by muscle fibers arranged in two layers: one in which the fibers encircle the esophagus and the outer one in which the muscle fibers run longitudinal to the esophagus. These are separated by the myenteric plexus, a nerve network which plays an important role in regulating and coordinating peristalsis.[2]

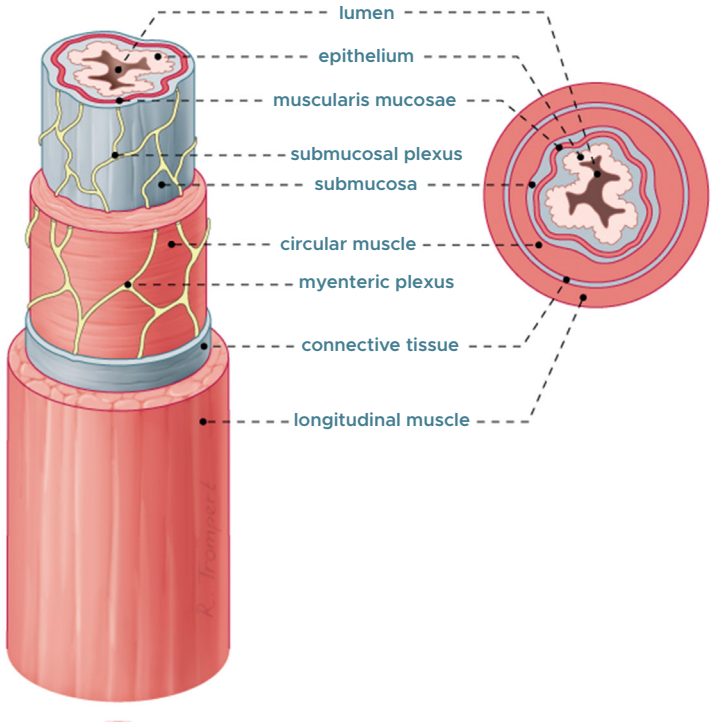

Figure 1. Layers of the esophageal wall.
(Original image by Rogier Trompert Medical art. All rights reserved)

Mediated by the vagal nerve and excitatory neurons of the myenteric plexus, a coordinated peristaltic contraction of the circular muscle layer facilitates bolus passage towards the stomach.[3] The esophageal body is enclosed at the top and bottom by two muscular rings, known respectively as the upper esophageal sphincter (UES) and the lower esophageal sphincter (LES) (Figure 2).[2] Both esophageal sphincters operate to close off the esophagus

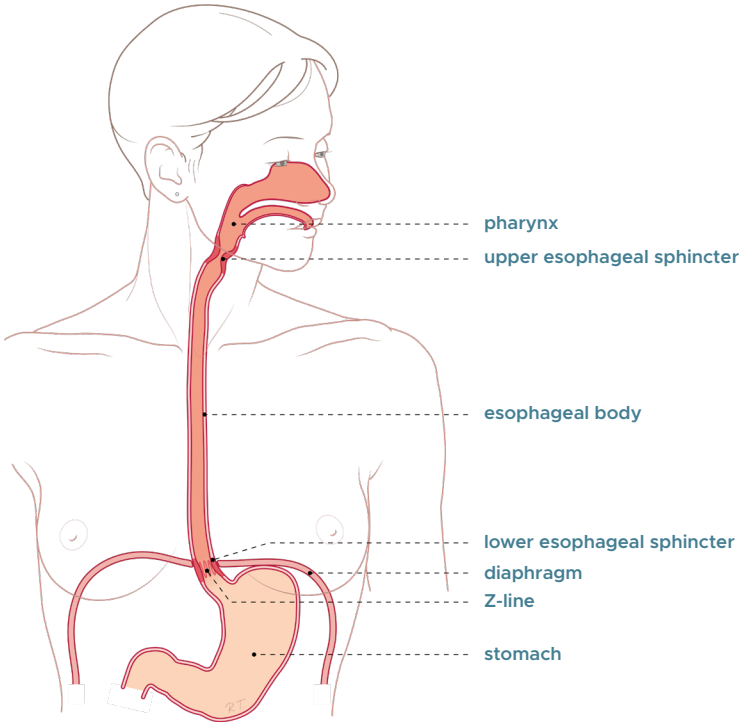

Figure 2. Schematic display of the anatomy of the esophagus.
(Original image by Rogier Trompert Medical art. All rights reserved)

when food is not being swallowed, yet should be able to relax briefly to facilitate bolus passage.[4] The UES is largely formed by the cricopharyngeal muscle and forms a barrier between the esophagus and the pharynx.[5] The LES is a thickened region of the circular muscle layer and surrounds the lower part of the esophagus. Together with the crural diaphragm, it forms the junction between the esophagus and the stomach, also known as the esophagogastric junction.[6]

The esophagogastric junction (EGJ) is a highly specialized region, consisting of the smooth muscle of the lower esophageal sphincter, surrounded by oblique gastric fibers that are anchored to the striated muscle of the diaphragm by the phreno-esophageal ligament. These structures act in concert and combine their tonic resting pressures to overrule the intra-abdominal pressure, preventing reflux of gastric contents into the esophagus.[7] Yet, the EGJ has to be able to relax briefly upon swallowing so that a bolus of food can enter the stomach and it should be able to open to allow retrograde passage of gastric contents into the esophagus in the occasion of vomiting or belching.[8] The combined coordinated actions of both esophageal sphincters together with the esophageal body are referred to as esophageal motility.

Esophageal dysfunction

Esophageal dysfunction occurs when normal esophageal peristalsis and/or function of one of the two esophageal sphincters is disturbed.[2] A variety of disorders result from esophageal dysfunction, and this thesis covers three of them: gastroesophageal reflux disease, achalasia and the inability to belch syndrome. The main goal of this thesis is to further unravel the pathophysiology and improve diagnostic and therapeutic strategies in these diseases. In part I of this thesis, we focus on the management of gastroesophageal reflux disease and related disorders such as giant paraesophageal hernia. Part II of this thesis covers achalasia, and offers practical considerations and guidelines for achalasia management. In part III of this thesis, we aim to improve our understanding of the pathogenesis of the inability to belch syndrome.

PART I GASTROESOPHAGEAL REFLUX DISEASE

When reflux of gastric contents across the EGJ into the esophagus occurs and causes troublesome symptoms or esophageal mucosal damage, it is referred to as gastroesophageal reflux disease (GERD).[9] GERD is one of the most prevalent gastrointestinal diseases in the western world, with typical symptoms such as regurgitation, heartburn or retrosternal pain reported at least occasionally by 20-25% of the general population.[10] The pathophysiology of GERD is multifactorial. Besides ineffective esophageal motility, visceral hypersensitivity and delayed gastric emptying, GERD most commonly is the result of incompetence of the EGJ. The two most important factors contributing to this incompetence are an increased prevalence of transient lower esophageal sphincter relaxations (TLESRs) and anatomical distortion of the LES and the crural diaphragm, also known as a hiatus hernia.[7,11]

Diagnosis

Several diagnostic tests can be used in the diagnostic work-up of patients with reflux symptoms. In the first line, proton pump inhibitors (PPIs) are often pragmatically started to evaluate whether the symptoms respond well to a trial of acid suppressive medication. If symptoms persist, patients tend to be referred to a gastroenterologist. PPI-refractory reflux symptoms are usually reason to perform an upper endoscopy.[9] In the first place, to exclude malignancies or other esophageal diseases such as eosinophilic esophagitis (EoE), but also to distinguish patients with macroscopic (erosive) esophagitis or a Barrett's esophagus from patients who lack any macroscopic signs. In **chapter 2** of this thesis, we investigate the utility of esophageal biopsies in patients with PPI-refractory reflux symptoms, in particular whether biopsies are required to exclude EoE, an inflammatory disorder of the esophagus in which the clinical presentation can resemble GERD.[12] Further investigation can be achieved through the use of ambulatory 24-hour pH (acidity) monitoring. This is an important diagnostic step in the evaluation of patients with refractory reflux symptoms, especially in those under consideration for anti-reflux surgery.[13] Standard catheter-based pH-studies can detect reflux episodes by detecting a drop in pH (<4). They are typically used

to determine whether there is a pathological esophageal acid exposure and whether there is a positive association between the onset of symptoms and reflux events, and therefore provide objective evidence whether the patients' symptoms are truly associated to reflux. Nowadays pH-studies are often combined with impedance monitoring, because this allows for the detection of weakly-acidic reflux episodes as well.[14] In the early '00s, a wireless pH monitoring device was developed. Instead of a catheter, it uses a radio-telemetric capsule temporarily attached to the esophageal mucosa.[15] It allows for a prolonged recording and has been shown to be generally better tolerated by patients, thereby increasing sensitivity for detecting reflux events.[16,17] In **chapter 3** we examine the added diagnostic value of wireless pH-monitoring for patients with nocturnal reflux symptoms.

Management

Initial GERD therapy is based on lifestyle interventions such as dietary restrictions, weight loss, head of the bed elevation and smoking cessation. Proton-pump inhibitor (PPI) therapy is the cornerstone of medical treatment in GERD, due to the favorable side effect profile and superior efficacy of PPIs in both symptom relief and healing of erosive esophagitis.[18] Alternative pharmacological therapies include antacids, histamine-receptor antagonists (H2RA), prokinetics and reflux inhibitors.[9] In **chapter 4** we study the effect of STW5 (Iberogast®) on reflux symptoms and investigated potential underlying mechanisms of action. In patients with therapy-refractory GERD, and a positive symptom-reflux association on the 24-hour pH-study, anti-reflux surgery can be considered. During this procedure, an anti-reflux barrier is created by wrapping the gastric fundus around the distal esophagus. This can be performed in 360 degrees (Nissen fundoplication) or partially, using a 270 degrees wrap (Toupet fundoplication).[19]

Giant paraesophageal hernia

In the situation of a hiatal hernia, the ability of the EGJ to prevent reflux is impeded, mainly as a result of the migration of the stomach through the diaphragmatic hiatus into the thoracic cavity. Manometrically, this can be observed as spatial separation of the two high-pressure zones of the LES and the crural diaphragm. Hiatal hernia can be categorized into the 'sliding' and the 'rolling' type, the latter is also known as a paraesophageal hernia. Paraesophageal hernias represent only 5% of all hiatal hernias and are characterized by a herniation of the gastric fundus adjacent to a normally positioned EGJ.[20,21] These hernias tend to be of considerable size, taking up great part of the thoracic cavity, also referred to as an intrathoracic stomach. The finding of an intrathoracic stomach is often incidental, but it is believed that potentially life-threatening complications may occur if the hernia is not surgically managed.[22] The indication for surgical repair of giant paraesophageal hernias has remained a topic of discussion for decades. Despite ongoing controversies, accurate information on the natural course of paraesophageal hernia is scarce. In **chapter 5** we were able to identify a substantial cohort of conservatively treated patients with giant paraesophageal hernia over almost

three decades. Our aim was to describe the long-term outcomes of these patients and to determine characteristics associated with clinical outcome.

PART II ACHALASIA

Whereas GERD may occur as a result of ineffective EGJ closure, the opposite end of the EGJ dysfunction spectrum is represented by another esophageal motility disorder. Achalasia is a rare and benign motor disorder of the esophagus characterized by insufficient lower esophageal sphincter relaxation and absence of peristalsis. Subsequent stasis of ingested foods results in symptoms such as dysphagia, regurgitation, chest pain and weight loss.[23] In achalasia, the ganglion cells in the myenteric plexus are destructed by an unknown cause. It is suggested that this may occur in genetically susceptible individuals after a viral infection that triggers an autoimmune response.[24]

As a result of new developments in achalasia patient care such as high-resolution manometry, per-oral endoscopic myotomy and studies providing new perspectives on achalasia subtypes, cancer risk and follow-up, there is a growing demand for standardized diagnostic and treatment protocols in achalasia management. Apart from consensus reports on isolated topics in achalasia management, there are no recent guidelines covering all aspects of the disease. Along with a European team of gastroenterologists, radiologists, and gastrointestinal surgeons, we developed an evidence-based framework with recommendations on the diagnosis, treatment and follow-up of adult achalasia patients. The result is the first European guidelines on achalasia, presented in **chapter 6**.

Diagnosis

A diagnosis of achalasia should be considered when patients present with dysphagia in combination with other esophageal symptoms, and when upper endoscopy has excluded alternative diagnoses. Barium esophagogram may reveal a classic ‘bird’s beak’ sign, a corkscrew appearance or esophageal dilation (Figure 3). High-resolution manometry (HRM) is considered being the golden standard for the diagnosis of esophageal motility disorders.[25] It measures intraluminal pressure in the esophageal body and stomach using a catheter with closely spaced pressure sensors. The manometric hallmarks for achalasia are incomplete relaxation of the LES, reflected by an increased integrative relaxation pressure, and absence of normal peristalsis. Based on the manometric contractility pattern of the esophageal body, three separate subtypes can be identified.[26]

Management

As the neuronal loss is irreversible, current treatment of achalasia is limited to reduction of symptoms and targeted at disabling the tonic contraction of the LES. Therapy through LES botulinum toxin injections is usually reserved for patients who are unfit for more invasive

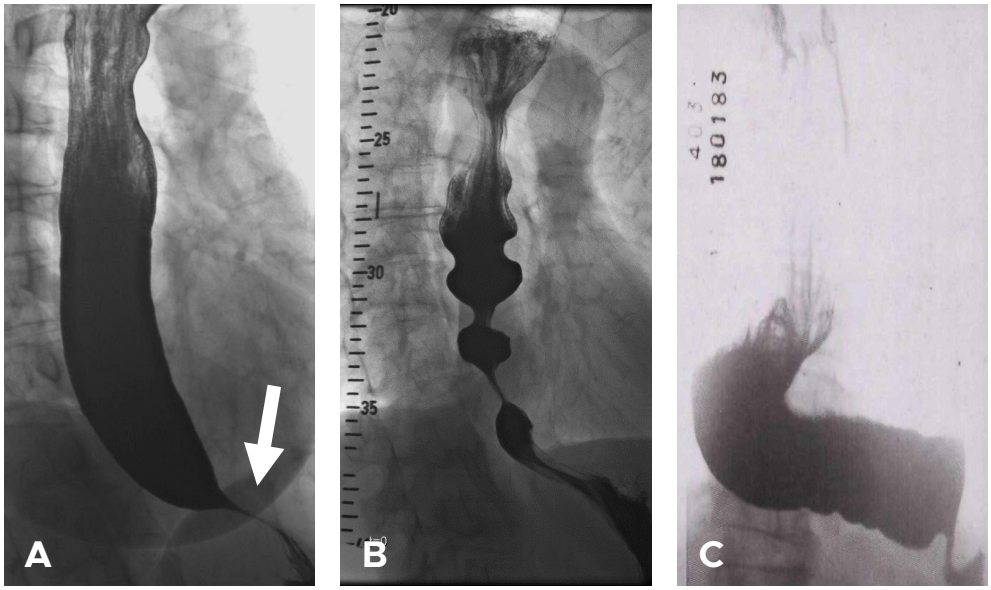

Figure 3. Typical findings of achalasia (a, bird's beak' sign; b, corkscrew appearance; c, esophageal dilation) on barium esophagogram.

treatments because of the limited duration of the pharmacological effect.[27] More definite therapies include laparoscopic Heller myotomy (LHM), per-oral endoscopic myotomy (POEM) and endoscopic pneumatic dilatation (PD). Overall, these therapies have comparable efficacy rates at a similar safety profile but have their own benefits and disadvantages.[28-30] More importantly, the success of treatment outcome appears to be dependent on individual patient characteristics.[31] Literature on these clinical predictors is extensive. In **chapter 7** we systematically assess all available literature on potential patient-specific predictors of achalasia treatment outcome. We examine the cumulative predictive values of several potential predictors, to provide a comprehensive overview and recommendations regarding a tailored treatment approach for the individual achalasia patient. Although achalasia treatment is considered to have a relatively good safety profile, in isolated cases perioperative complications may occur. In the case of PD, esophageal perforation is considered the most serious complication.[32] **Chapter 8** describes our experience with two relatively new endoscopic techniques for the management of iatrogenic perforation in a series of achalasia patients with esophageal perforation after PD.

PART III INABILITY TO BELCH SYNDROME

The UES is formed by the cricopharyngeal muscle, part of the inferior pharyngeal constrictor and is closely related to the cricoid cartilage and the anterior larynx.[33] Opening of the UES is triggered by swallowing, or retrogradely, by the belching reflex.[5,34] In healthy volunteers, intragastric air enters the esophagus during a TLESR, which leads to a rapid esophageal pressure increase to the level of the intragastric pressure, also known as the common cavity phenomenon.[35] The sudden distention of the esophageal body stimulates the stress receptors in the esophageal wall that will initiate UES relaxation and expulsion of air.[34]

Inablity to belch syndrome

Whereas frequent or excessive belching associated with gastroesophageal reflux disease or functional dyspepsia is one of the most common gastrointestinal symptoms in daily practice, a small subset of patients referred to gastrointestinal or otorhinolaryngological practices, suffers from the exact opposite problem; esophageal and abdominal symptoms caused by an inability to belch.[36] Inability to belch can be seen as part of the gas-bloating syndrome, which can arise post-fundoplication, or as an inability to belch from esophagus to oropharynx. The latter phenomenon is rarely reported in medical literature, and the underlying etiology is virtually unknown. In the past few years, an increasing number of patients have been seeking medical attention because of a self-reported inability to belch in combination with esophageal or abdominal symptoms. In **chapter 9** we investigate the pathophysiological mechanisms of inability to belch using concurrent high-resolution manometry and impedance monitoring.

OUTLINE OF THIS THESIS

This thesis covers studies on three esophageal motility disorders. The primary aim of this thesis is to further clarify the etiology and pathophysiology of these disorders, and to optimize patient care. We particularly focus on 1) the added value of alternative diagnostic tools and therapeutics in the management of gastroesophageal reflux disease, 2) practical considerations and guidelines in the management of achalasia, and 3) the underlying pathophysiology of the inability to belch syndrome.

The first part of this thesis focuses on GERD management. **Chapter 2** presents a prospective study in which the utility of esophageal biopsy sampling in the diagnosis of refractory reflux symptoms is studied. In **chapter 3** we use prolonged wireless pH-monitoring to investigate a group of patients with nocturnal reflux symptoms and aim to clarify the added diagnostic value of prolonged recording. Through a randomized controlled trial in **chapter 4**, a potential new therapeutic agent in the treatment of heartburn in dyspeptic patients is evaluated. The natural history of giant paraesophageal hernia is investigated in **chapter 5**. The second part of this thesis focuses on achalasia and offers practical considerations and guidelines for achalasia management. **Chapter 6** contains the European guideline on achalasia diagnosis,

treatment and follow-up. In **chapter 7** a systematic review and meta-analysis aims to identify all available potential clinical predictors of achalasia treatment outcome. **Chapter 8** describes our experience with endoscopic treatment for iatrogenic perforation after pneumatic dilatation in a case series of adult achalasia patients. The third part of this thesis focuses on the etiology of the relatively unknown phenomenon of an inability to belch. In **chapter 9** we examine patients with symptoms of inability to belch and study the role of the UES before and after botox injections. In **chapter 10** we discuss the implications for future research and patient care based on the findings of this thesis.

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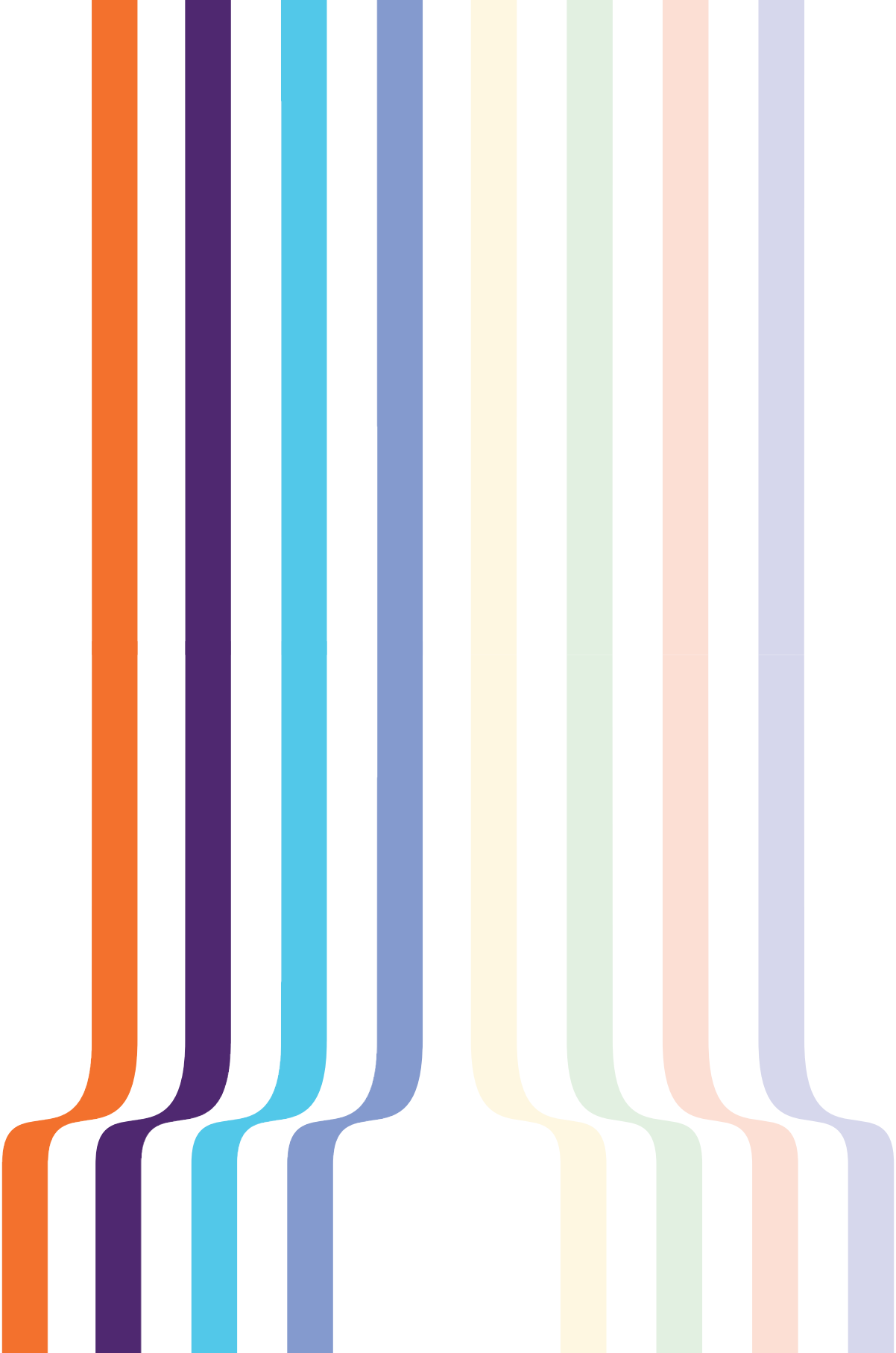
PART I

GASTROESOPHAGEAL REFLUX DISEASE



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3

Utility of routine esophageal biopsies in patients with refractory reflux symptoms

Renske A.B. Oude Nijhuis, Wouter L. Curvers, Mirjam van der Ende, Thomas V.K. Herregods, Jeroen M. Schuitenmaker, Andreas J.P.M. Smout and Albert J. Bredenoord

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ABSTRACT

Background

This study aimed to assess the diagnostic yield of routine esophageal biopsies in patients with refractory reflux symptoms.

Methods

We prospectively enrolled consecutive patients referred for upper endoscopy and collected histological, clinical, and endoscopic data.

Results

Of the 301 included patients, 14 (4.7%) patients met the clinicopathological diagnostic definition of eosinophilic esophagitis. Presence of dysphagia, food bolus impaction, atopic background, and typical endoscopic features were the factors with the strongest association and diagnostic accuracy for eosinophilic esophagitis. The diagnostic yield in patients lacking symptoms of dysphagia or endoscopic features was negligible (0% and 1.9%, respectively).

Discussion

Routine esophageal biopsy sampling in patients with refractory reflux symptoms has a low diagnostic yield. Esophageal biopsies should only be obtained in patients with refractory reflux symptoms who also present with dysphagia.

INTRODUCTION

Reflux symptoms refractory to proton-pump inhibitors (PPIs) are common and a frequent reason for referral for upper endoscopy.[1,2] Until recently, routine esophageal biopsy sampling was not recommended in these patients. In the most recent version of the Rome criteria, however, it is stated that esophageal biopsies should be obtained in all patients with refractory reflux symptoms to rule out eosinophilic esophagitis (EoE).[3] Evidence underpinning this recommendation is lacking, while obtaining biopsies in every suspected reflux patient would lead to an extremely high volume of biopsies, resulting in higher medical costs, increased risk of complications, and longer procedure times.[4] We aimed to assess the yield of routine esophageal biopsies in patients with refractory reflux symptoms and to determine the clinical factors associated with EoE diagnosis.

METHODS

We performed a prospective cross-sectional study of adult patients with reflux symptoms (i.e., heartburn, regurgitation, and/or chest pain) for at least 3 months and ≥3 times a week under standard-dose PPI therapy.[5] Consecutive patients from 2 teaching hospitals were enrolled between April 2018 and April 2020, and they underwent upper endoscopy per standardized protocol. Because esophageal eosinophilia in EoE can be patchy, multiple biopsy specimens were obtained from several esophageal levels as recommended by current guidelines.[6] Patients with preexistent esophageal disorders were excluded. All patients underwent a complete symptom assessment using validated questionnaires.[7–9] Clinical information and endoscopic findings were recorded. The study was approved by the local ethics committee (W18_061#18.079). Statistical analysis was performed with SPSS, version 24 (SPSS, Chicago, IL).

RESULTS

A total of 301 patients (40.5% male; mean age 56.0 ± 16.4 years) were included. Fourteen patients (4.7%, 95% confidence interval (CI) (2.6–7.7)) met the clinicopathological diagnostic definition of EoE. Clinical, endoscopic, and histological characteristics are presented for the total study population and stratified for EoE diagnosis in **Table 1**. Symptoms of dysphagia, food impaction and vomiting, a history of endoscopic bolus dislodgement, atopic background, and presence of typical endoscopic features were more frequently identified in EoE patients (all $P < 0.05$). All 14 EoE patients presented with symptoms of dysphagia, and in 9 (64.3%) patients endoscopic features were present (**Table 2**). In EoE patients, the median number of eosinophils was 34 (19–53) per microscopic high-power field. There were no significant differences in the degree of eosinophilia for the different levels of the esophagus ($P > 0.87$). Diagnostic yield was calculated for different patient subgroups (**Table 3**). The yield of routine esophageal biopsy sampling for the detection of EoE in patients with refractory reflux symptoms who also presented with dysphagia was 9.2%. Applying these criteria, no EoE

Table 1. Clinical, endoscopic, and histological findings of included patients stratified for EoE diagnosis

	Total study population (*n* = 301)		Non-EoE patients	EoE patients	
Clinical characteristics	*n*	%	(*n* = 287) *n* (%)	(*n* = 14) *n* (%)	P value
Sex					
Male	222	40.5	113 (39.4)	9 (64.3)	0.064
Female	179	59.5	174 (60.6)	5 (35.7)	
Age at inclusion (yr), mean ± SD	56.0 ± 16.4		56.7 ± 16.0	40.8 ± 18.7	**<0.001**
Caucasian	248	82.4	235 (81.9)	13 (92.9)	0.292
BMI, mean ± SD	26.0 ± 4.2		26.1 ± 4.3	23.1 (1.2)	**<0.001**
Atopic background	70/301	23.3	58/287 (20.2)	12/14 (85.7)	**<0.001**
Asthma	30	42.9	26 (44.8)	4 (33.3)	
Allergic rhinoconjunctivitis	22	31.4	18 (31.0)	4 (33.3)	
Food allergies	11	15.7	8 (13.8)	3 (25.0)	
Eczema	7	10.0	5 (8.6)	2 (16.7)	
Allergic skin allergies	4	5.7	4 (6.9)	0 (0)	
Intoxications					
History of smoking	68	22.6	66 (23.0)	2 (14.3)	0.447
Alcohol use >2 units per day	22	7.3	22 (7.7)	0 (0)	0.282
Symptoms at presentation					
Heartburn	185	61.5	177 (61.7)	8 (57.1)	0.734
Dysphagia	153	50.8	139 (48.8)	14 (100)	**<0.001**
Regurgitation	125	41.5	121 (42.2)	4 (28.6)	0.314
Epigastric pain	116	38.5	114 (39.7)	2 (14.3)	0.056
Chest pain	92	30.6	85 (29.6)	7 (50.0)	0.136
Symptoms of food impaction	58	19.3	49 (17.1)	9 (64.3)	**<0.001**

Globus	28	9.3	28 (9.8)	0 (0)	0.378
Vomiting	18	6.0	15 (5.2)	3 (21.4)	**0.043**
Respiratory symptoms	11	3.7	11 (3.8)	0 (0)	0.587
Duration of symptoms (mo), median (IQR)	2 (0–5)		1 (0–5)	5 (0.8–10)	0.072
History of endoscopic bolus dislodgement	9	3.0	6 (2.1)	3 (21.4)	**0.003**
Symptom scores					
RDQ, median (IQR)	1.5 (0.7–2.7)		1.5 (0.7–2.7)	1.3 (0.5–1.8)	0.260
SDI, median (IQR)	3.0 (0–5.0)		3.0 (0–5.0)	5.0 (3.8–5.3)	**0.011**
BEDQ, median (IQR)	5.0 (0–11.0)		5.0 (0–11.0)	7.0 (4.5–13.0)	0.102
Endoscopic findings					
Endoscopic features of EoE	44	14.6	35 (12.2)	9 (64.3)	**<0.001**
Rings	27	9.0	21 (7.3)	6 (42.9)	
Furrows	16	5.3	11 (3.8)	5 (35.7)	
White exudates	16	5.3	10 (3.5)	6 (42.9)	
Crepe paper esophagus	2	0.7	1 (0.3)	1 (7.14)	
Edema	2	0.7	2 (0.7)	0 (0)	
Strictures	5	1.7	2 (0.7)	3 (21.4)	
EREFS score, median (IQR)	0 (0–0)		0 (0–0)	1 (0–3)	**<0.001**

Table continues on next page

Table 1 continued

Clinical characteristics	Total study population (*n* = 301) *n*	%	Non-EoE patients (*n* = 287) *n* (%)	EoE patients (*n* = 14) *n* (%)	P value
Other endoscopic findings					
Reflux esophagitis	55/301	18.3	54/287 (18.8)[a]	1/14 (7.1)	0.478
Grade A	32	58.2	32 (59.3)	0 (0)	
Grade B	19	34.5	19 (35.2)	0 (0)	
Grade C	4	7.3	3 (5.6)	1 (7.1)	
Grade D	-	-	-	-	
Hiatal hernia	106	35.2	104 (36.2)	2 (14.3)	0.150
Barrett's esophagus	22	7.3	22 (7.7)	0 (0)	0.610
Schatzki ring	20	6.6	17 (5.9)	3 (21.4)	0.057
Gastrointestinal ulcer(s)	6	2.0	6 (2.1)	0 (0)	0.750
Esophageal cancer	2	0.7	2 (0.7)	0/15 (0%)	0.750
Histological findings					
Peak eosinophil count (eos/HPF), median (IQR)	0 (0–0)		0 (0–0)	34 (19–53)	**<0.001**
Basal cell hyperplasia	12	4.0	9 (3.1)	3 (21.4)	**0.014**
Spongiosis	9	3.0	5 (1.7)	4 (28.6)	**<0.001**
Microabscesses	4	1.3	1 (0.3)	4 (75.0)	**<0.001**
Histology-confirmed candida infection	5	1.7	5 (1.7)	0 (0)	0.787

Bold values mean statistically significant values, a P value of, 0.05 was considered statistically significant.BEDQ, Brief Esophageal Dysphagia Questionnaire; BMI, body mass index; EoE, eosinophilic esophagitis; eos/HPF, eosinophils per microscopic high-power field; IQR, interquartile range; *N*, number of patients; RDQ, Reflux Disease Questionnaire; SDI, Straumann Dysphagia Index.

[a]Additional data on clinical findings stratified for the presence of typical endoscopic features in the non-EoE population can be found in Supplemental Table 1.

Table 2. Individual characteristics of the 14 patients diagnosed with eosinophilic esophagitis

	Age	Sex	Dysphagia	Atopy	Endoscopic signs	Symptoms of food impaction	Endoscopic bolus removal
1	30	M	+	+	+	+	+
2	43	F	+	+	+	+	+
3	26	F	+	+	+	+	+
4	54	M	+	+	+	+	+
5	64	M	+	+	+	+	-
6	21	M	+	+	+	+	-
7	42	F	+	+	+	-	-
8	20	M	+	+	+	-	-
9	37	M	+	+	+	-	-
10	33	F	+	+	-	+	-
11	62	F	+	+	-	-	-
12	32	M	+	+	-	-	-
13	83	M	+	-	-	+	-
14	24	F	+	-	-	+	-

+ characteristic present
- characteristic absent

patient would have been missed. If patients who presented with both dysphagia and typical endoscopic features of EoE were analyzed, the diagnostic yield increased to 30.0%, but 5 patients would have been missed. In the subgroup of patients lacking endoscopic features, or dysphagia, the diagnostic yield was 1.9% and 0%, respectively. Routine biopsies in patients who presented with dysphagia but lacked endoscopic features led to a diagnostic yield of 4.1%.

Diagnostic performance of the relevant patient characteristics is presented in **Table 3**. Dysphagia was highly sensitive for EoE (100%), whereas history of endoscopic bolus dislodgement had the highest diagnostic accuracy for EoE diagnosis (94%). Atopic background (odds ratio (OR) 23.7; 95% CI 5.2–108.8), typical endoscopic features (OR 13.0; 95% CI 4.1–40.9), and a history of endoscopic bolus dislodgement (OR 12.8; 95% CI 2.8–57.9) were identified as the factors with the strongest association.

Table 3. Individual characteristics of the 14 patients diagnosed with eosinophilic esophagitis

		EoE patients						
Characteristic	***n/N***	**missed, *n***	**Sensitivity**	**Specificity**	**Accuracy**	**PPV**	**NPV**	**OR**
Dysphagia	14/153	0	100.0 (76.8–100.0)	52.6 (45.6–57.5)	53.8 (48.0–59.6)	9.2 (8.2–10.2)	100.0	[a]
Vomiting	3/18	11	21.4 (4.7–50.8)	94.8 (91.5–97.1)	91.3 (87.6–94.3)	16.7 (6.1–37.9)	96.1 (95.0–97.0)	4.9 (1.2–9.3)
Symptoms of food impaction	9/58	5	64.3 (35.1–87.2)	82.9 (78.1–87.1)	82.1 (77.3–86.2)	15.5 (10.3–22.7)	97.9 (95.9–99.0)	8.7 (2.8–27.2)
History of endoscopic bolus removal	3/9	11	21.4 (4.7–50.8)	97.9 (95.5–99.2)	94.4 (91.1–96.7)	33.3 (12.2–64.2)	96.2 (95.1–97.1)	12.8 (1.2–19.6)
Atopy	12/70	2	85.7 (57.2–98.2)	79.8 (74.7–84.3)	80.1 (75.1–84.4)	17.1 (13.1–22.1)	99.1 (96.9–99.8)	23.7 (5.2–108)
Endoscopic features	9/44	5	64.3 (35.1–87.2)	87.8 (83.5–91.4)	86.7 (82.4–90.3)	20.5 (13.5–29.8)	98.1 (96.1–99.0)	13.0 (4.1–40.9)
Schatzki ring	3/17	11	21.4 (4.7–50.8)	94.1 (90.7–96.5)	90.7 (86.8–93.7)	15.0 (5.5–34.7)	96 (94.9–97.0)	4.3 (1.1–17.0)

Values are presented as % with 95% CI. Diagnostic performance of the combination of multiple factors are shown in Supplemental Table 2.

CI, confidence interval, EoE, eosinophilic esophagitis; *n*, number of EoE cases; *N*, sample size; NPV, negative predictive values; OR, odds ratio; PPV, positive predictive value.

[a]For binary variables with a zero cell count in the contingency table, logistic regression analysis was not performed.

DISCUSSION

This study implements the recommendation to biopsy every patient with refractory reflux symptoms in clinical practice and provides evidence that its utility is low. Diagnostic yield in patients lacking dysphagia or any other typical EoE hallmark was even negligible (0% and 1.9%, respectively).

At present, there are a few small studies demonstrating an EoE prevalence between 0.9% and 4% in patients with PPI-refractory reflux symptoms.[10,11] Mackenzie *et al.*[12] diagnosed EoE in 12% of the patients who presented with dysphagia, as being in accordance with the prevalence of 9% that we found in patients with both dysphagia and reflux symptoms. An essential question ensuing from this is, what is the best cutoff prevalence that justifies esophageal biopsy sampling? Miller *et al.*[13] evaluated the cost-effectiveness of endoscopic biopsy sampling for EoE in a hypothetical cohort of patients with refractory reflux symptoms. The authors concluded that routine esophageal biopsy sampling in this population is only cost-effective when EoE prevalence exceeds 8%.

Considering our findings, we strongly argue against routine esophageal biopsy sampling in all patients with refractory reflux symptoms. Rather, biopsies should be obtained only if patients exhibit specific clinical characteristics suggestive of EoE. The determinant with the highest sensitivity, in this case dysphagia, should be used for accurate patient selection. Theoretically, one could narrow down this group even further by selecting patients based on clinical characteristics with a high specificity such as typical endoscopic features or atopic background. In clinical practice, however, complicated algorithms and checklists have limited usability. Therefore, we recommend esophageal biopsy sampling in reflux patients who also present with dysphagia; in this way, no diagnoses are missed while the number of abundant biopsies is minimized. This study has some limitations. First, biopsy sampling was performed under PPI therapy while a minority of EoE patients are thought to respond to PPIs.[6] Although this is a drawback of our study, the percentage of PPI-responsive EoE in patients with typical reflux symptoms, without a priori suspicion of EoE, is thought to be very low and it is unlikely that this seriously affected our results. Second, because of low EoE prevalence, our sample size was insufficient to perform multivariate risk modeling. Nevertheless, using an alternative approach, we identified several easy-to-observe patient characteristics that can guide endoscopists to select eligible patients for esophageal biopsy sampling.

In conclusion, routine esophageal biopsy sampling has a very low diagnostic yield in patients with refractory reflux symptoms. Our data show that esophageal biopsies should only be obtained in patients with refractory reflux symptoms who also present with symptoms of dysphagia because this increases the diagnostic yield to 9.2% and reduces the total volume of biopsies by half while no EoE cases are missed.

AUTHOR CONTRIBUTIONS

R.A.B.O.N., A.J.B., T.V.K.H., and A.J.P.M.S. played a role in planning of the study. R.A.B.O.N., W.L.C., and A.J.B. had a role in conducting the study. R.A.B.O.N. and M.v.d.E. were involved in the acquisition of data. R.A.B.O.N., T.V.K.H., J.M.S. and A.J.B. had a role in collecting and/or interpreting data. R.A.B.O.N. played a role in drafting the manuscript. A.J.B., W.L.C., T.V.K.H., J.M.S., A.J.P.M.S., and A.J.B. played a role in reviewing and revising the manuscript for important intellectual content. All authors approved the final draft submitted.

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Clinical, endoscopic and histological findings stratified for the presence of typical endoscopic features in non-EoE patients (*n* = 287)

	Endoscopic features of EoE		
Clinical characteristics	**Present (*n* = 35)**	**Absent (*n* = 252)**	**P value**
Symptoms at presentation			
Heartburn	20 (57.1)	157 (62.3)	0.556
Dysphagia	21 (60.0)	118 (46.8)	0.144
Regurgitation	13 (37.1)	108 (42.9)	0.521
Epigastric pain	13 (37.1)	101 (40.1)	0.739
Chest pain	14 (40.0)	71 (28.2)	0.151
Symptoms of food impaction	9 (25.7)	40 (15.9)	0.147
Globus	1 (2.9)	27 (10.7)	0.142
Vomiting	2 (5.7)	13 (5.2)	0.890
Respiratory symptoms	0 (0)	11 (4.4)	0.233
Relevant medical history			
Atopic background	5 (14.3)	53 (21.0)	0.352
History of endoscopic bolus dislodgement	3 (8.6)	3 (1.2)	**0.026**
Endoscopic characteristics			
Features of EoE			
Rings	21 (60.0)	-	-
Furrows	11 (31.4)	-	-
White exudates	10 (28.6)	-	-
Crepe paper esophagus	1 (2.9)	-	-
Edema	2 (5.7)	-	-
Strictures	2 (5.7)	-	-
Other endoscopic findings			
Reflux esophagitis	6 (17.1)	48 (19.0)	0.787
Hiatal hernia	12 (34.3)	92 (36.5)	0.798
Barrett's esophagus	0 (0)	22 (8.7)	0.051
Schatzki ring	5 (14.3)	12 (4.8)	**0.042**
Gastrointestinal ulcer(s)	1 (2.9)	5 (2.0)	0.545
Esophageal cancer	0 (0)	2 (0.8)	0.771
Histological characteristics			
Peak eosinophil count (eos/HPF), median (IQR)	0 (0-0)	0 (0-0)	0.589
Basal cell hyperplasia	1 (2.9)	8 (3.2)	0.698
Spongiosis	2 (5.7)	3 (1.2)	0.114
Microabscesses	1 (2.9)	0 (0)	0.122
Histology-confirmed candida infection	0 (0)	5 (2.0)	0.519

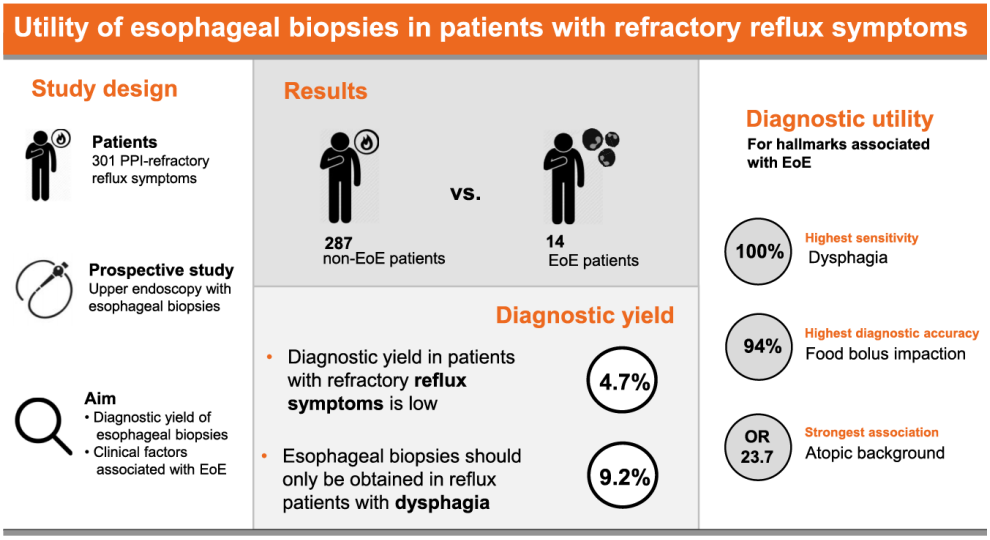
EoE, eosinophilic esophagitis; IQR, interquartile range; *N*,number of patients; SD, standard deviation; eos/HPF, eosinophils per microscopic high-power field.

Supplemental Table 2. Diagnostic performance of multiple characteristics for EoE diagnosis in the study population (*n* = 301)

		EoE patients					
Characteristic	***n/N***	**missed, *n***	**Sensitivity**	**Specificity**	**Accuracy**	**PPV**	**NPV**
Dysphagia + endoscopic signs	9/30	5	64.3 (35.1-87.2)	77.7 (69.9-84.3)	83.0 (76.1-88.6)	30.0 (19.8-42.7)	96.0 (92.1-98.0)
Dysphagia + history of endoscopic bolus removal	3/8	11	21.4 (4.6-50.8)	96.4 (91.8-98.8)	89.5 (83.6-93.9)	37.5 (13.8-69.2)	92.4 (90.2-94.1)
Dysphagia + atopy	12/39	2	85.7 (57.2-98.2)	80.6 (73.0-86.8)	81.1 (73.9-86.9)	30.7 (23.0-40.0)	98.3 (93.9-99.5)
Dysphagia + atopy + history of endoscopic bolus removal	12/44	2	85.7 (57.2-98.2)	77.0 (69.1-83.7)	77.8 (70.4-84.1)	27.3 (20.6-35.2)	98.2 (93.7-99.5)

Values are presented as percentages with 95% confidence interval.

CI, confidence interval, EoE, eosinophilic esophagitis; *n*, number of EoE cases; *N*, number of study sample; NPV, negative predictive values; PPV, positive predictive value.



Supplemental Figure 1. Visual abstract

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Characterization of patients with nighttime reflux symptoms: observations made with prolonged wireless esophageal pH monitoring

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ABSTRACT

Background

Although nighttime reflux symptoms are common, the presence of nocturnal reflux is seldom confirmed with a standard 24 hours pH study.

Aim

To study patients with supine nighttime reflux symptoms using prolonged wireless pH monitoring.

Methods

In this retrospective study, patients with typical acid reflux symptoms were studied using 96-h pH monitoring. Patients with nighttime reflux symptoms were compared to those without. Night-to-night variability and diagnostic accuracy of 24-, 48- and 72-hours pH studies compared to the 96-hours "gold standard" were evaluated.

Results

Of the 105 included patients (61.9% females; mean age 46.8 ± 14.4 years), 86 (81.9%) reported nighttime reflux symptoms, of which 67.4% had pathological supine nocturnal acid exposure in at least one night. There was high variance in night-to-night acid exposure (94% (IQR0-144)), which was larger than the variance in upright acid exposure (58% (IQR32-88); $P < 0.001$). When analyzing the first 24 hours of the pH study, 32% of patients were diagnosed with pathological supine nighttime acid exposure versus 51% of patients based upon the 96-hours pH-test. The diagnostic accuracy and yield improved with study duration ($P < 0.001$). Reflux episodes with a lower nadir pH or longer acid clearance time were more prone to provoke nightly symptoms.

Conclusions

The majority of patients with nocturnal reflux symptoms had pathological acid exposure in at least one night of the prolonged pH recording. A high night-to-night variability in acid exposure reduces the clinical value and diagnostic yield of pH monitoring limited to 24 hours. Prolonged testing is a more appropriate diagnostic tool for patients with nocturnal reflux symptoms.

INTRODUCTION

Nighttime reflux symptoms are common in the general population; it has been estimated that approximately 50% of individuals who suffer from generalized reflux symptoms, also experience nighttime symptoms, disturbing sleep and daytime functioning.[1-3] Conversely, poor sleep quality and arousal from sleep have been shown to evoke reflux as well, underlining the complex relationship between sleep and reflux.[4,5] Although the last years' progress has been made in our understanding of the pathogenesis of nocturnal reflux, several questions remain unanswered and patients with nocturnal reflux symptoms are still an underreported group in the current literature.[2,4,6]

In patients with nighttime reflux symptoms referred for ambulatory pH monitoring, the diagnosis of nocturnal reflux is seldom confirmed. One could argue, however, that a traditional 24-hour catheter-based system is not the appropriate diagnostic tool to identify nocturnal reflux. Gastroesophageal reflux occurs multiple times during the day, also in healthy subjects.[7,8] In patients with gastroesophageal reflux disease (GERD), the incidence of daytime reflux episodes is often increased and this usually causes multiple symptoms during the day. Nighttime reflux occurs less frequently, both in healthy asymptomatic subjects and in patients.[6,8,9] However, when nocturnal reflux does occur, these episodes are commonly associated with prolonged esophageal acid exposure due to reduced acid clearing mechanisms at night, frequently resulting in mucosal damage such as reflux esophagitis and severe symptoms leading to sleep arousal, poor sleep quality and excessive heartburn.[10] In other words, although a single nocturnal reflux episode can alter the clinical diagnosis of a 24-hour study, the likelihood of detecting it is low, which may result in a falsely negative study report in a substantial subset of patients. In addition, the very nature of catheter-based pH systems influences comfort and sleeping behavior, which minimizes the occurrence of nocturnal reflux.[11] We hypothesize that patients with nocturnal reflux symptoms may benefit from prolonged pH monitoring because of improved sensitivity. Wireless pH study uses a radio-telemetric capsule temporarily attached to the esophageal mucosa. It allows for a prolonged recording and has been shown to be generally better tolerated by patients, thereby increasing sensitivity for detecting reflux events.[12-15] Intuitively, it is presumed that this improved sensitivity extends to nocturnal reflux. In this study, we aimed to explore this concept. Our primary objective was to evaluate the added diagnostic value and reproducibility of prolonged pH testing for the presence of nocturnal reflux. Our second objective was to study patients with nocturnal reflux, specifically prevalence, clinical characteristics and symptom perception.

MATERIALS AND METHODS

Subjects

In this retrospective study, patients with daytime and/or supine nighttime reflux symptoms referred for prolonged wireless pH monitoring, primarily in the work-up of anti-reflux surgery,

were studied at a tertiary referral center (University College London, London) between January 2017 and December 2020. A requirement for inclusion was the presence of typical reflux symptoms (heartburn, regurgitation and/or chest pain) as a primary presenting complaint. A complete medical history was undertaken prior to the pH study in all patients. Patients with a history of esophageal or gastric surgery or other known esophageal diseases were excluded. Acid-suppressive medication and drugs that affected esophageal motility (eg, prokinetics and sedatives) were discontinued for at least 7 days prior to all pH studies. Patients with a nocturnal work (or reversed sleep) pattern, a technical unsuccessful study or with capsule detachment prior to 72 hours, were excluded. The study protocol was submitted to the local Institutional Review Board and formal evaluation was waived (reference number W21_004 # 21.006).

Prolonged wireless pH monitoring

A wireless pH system (Bravo, Medtronic) was calibrated and a radio-telemetry capsule was placed 6 cm proximal to the Z-line as described in the literature.[15] The capsule was attached while patients were under sedation during endoscopy as per standard protocol. Patients were instructed to press the event marker button on the pH data logger whenever they experienced a pre-assigned reflux symptom. Subjects were encouraged to maintain their normal daily activities, consume their usual meals and were asked to mark the period spent in the supine position. After 96 hours, patients returned the recording device for downloading of the data.

Data analysis

We defined “night” “nighttime” or “nocturnal” as the (patient-reported) period of >3 continuous hours with an onset between 8 pm and 8 am, spent in the supine position. Periods in the supine position during the day (ie, naps) were excluded from the analysis. Total acid exposure was considered pathological if it was found to be >6% and supine nocturnal acid exposure was defined as pathological if >1.5%.[16] Variance was calculated as the deviation of the 24-, 48- or 72-hour values from the overall 96-hour result and the coefficient of variation was calculated as the ratio of the standard deviation to the mean. The Symptom Index (SI) was calculated as the percentage of symptoms related to reflux (diagnostic cut-off >50%). For each patient, the acid exposure time (AET), the total number of acidic reflux events, SI, diagnostic accuracy and day-to-day variability were calculated cumulatively for the first 24-, 48-, 72- and entire 96 hours overall and for days and nights separately.

Statistical analysis

Descriptive statistics were presented as the percentage for categorical data and as mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables. Mann–Whitney U or chi-squared tests were used to analyze variables between groups. Paired data were compared using the Wilcoxon signed-rank test, Friedman test and Cochran’s Q test when appropriate. To explore factors associated with the occurrence of supine nocturnal

reflux, logistic regression analysis was performed. SPSS Statistics (ver. 24; SPSS) was used for statistical analysis.

RESULTS

Study population

A total of 162 patients underwent wireless pH monitoring for their reflux symptoms. After an initial screening and the removal of duplicates, 130 eligible pH studies were assessed. Patients with incomplete or missing documentation (*n* = 19) or a history of esophageal surgery (*n* = 6) were excluded (**Figure 1**). As a result, analysis was completed in 105 patients. All patients (61.9% females; mean age 46.8 ± 14.4 years) reported typical symptoms (heartburn, 84.8%; regurgitation, 65.7%; and/or chest pain, 31.4%) and a proportion reported additional atypical symptoms including cough (29.5%) and belching (24.8%). At upper endoscopy, reflux esophagitis was found in 20 (19.0%) patients.

Supine nocturnal gastroesophageal reflux

The median overall recording time of the pH studies was 80:09 hours (IQR 74:15-84:56), with a median nocturnal recording time of 31:16 hours (IQR 27:20-36:09) across 4 days. Complete recordings of four consecutive nights were available in the majority (78.1%) of patients. A total of 8591 acidic reflux episodes were manually detected and analyzed. Of these, 917 (10.7%)

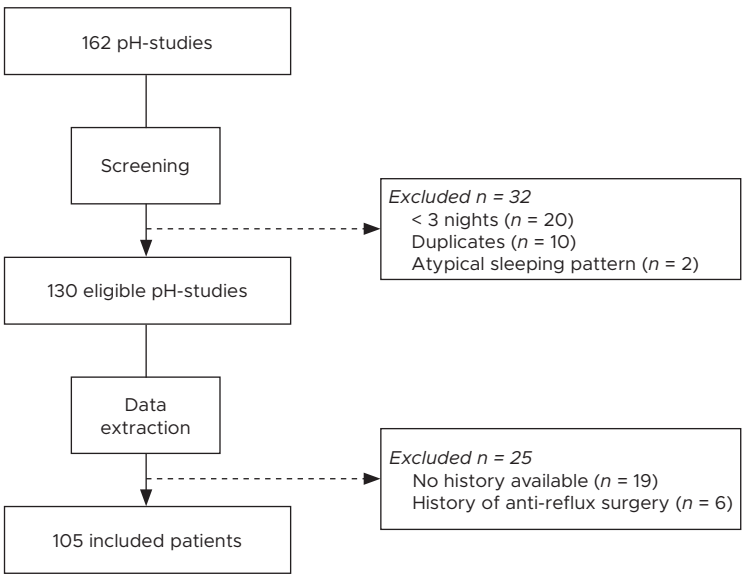

Figure 1. Flowchart of case finding

occurred in the night and 7674 (89.3%) during the day. A median of 75 (35-111) acidic reflux episodes were found per patient, of which a small proportion (5 (1-12)) was supine nocturnal reflux episodes. Patients had a median AET of 5.6% (2.1-9.4), with 6.8% (2.4-13.3) during the day and 1.4% (0.0-5.0) during the night. Based upon the total recording, 49 patients (46.7%) had a pathological total acid exposure. In 53 (50.5%) patients, a pathological supine nighttime acid exposure over 96 hours was observed.

Clinical characteristics of subjects with self-reported nocturnal symptoms

Of the included patients, 86 (81.9%) reported nighttime reflux symptoms. **Table 1** shows the clinical characteristics stratified for the presence of self-reported nocturnal reflux symptoms. Patients that explicitly reported nighttime symptoms were found to have both, greater supine nighttime acid exposure ($P < 0.01$) and increased number of acidic reflux episodes ($P < 0.01$). Moreover, nocturnal reflux symptoms were predominantly reported by male patients ($P < 0.030$). In patients with nocturnal symptoms, heartburn and chest pain were more frequently reported (both $P < 0.030$). Of the patients with self-reported nocturnal reflux symptoms, 74 (86.0%) patients had at least one reflux episode in at least one of the four nights, versus 10 (52.6%) of the patients without nighttime symptoms ($P < 0.001$). In 12 (14.0%) patients with nocturnal symptoms, no supine nighttime reflux events were identified for the entire recording. When assessing the first recorded night of patients with nocturnal symptoms, 43 (50.0%) patients had no supine nighttime reflux events at all, but in the majority (51.2%) of these patients, reflux eventually occurred at a later moment during the 96-hour recording. As for the presence of pathological supine nighttime acid exposure (>1.5%), 58 (67.4%) patients with nocturnal symptoms had an abnormal acid exposure in at least one of the nights. Of these patients, only nine (15.1%) had a pathological acid exposure for all nights, while in the majority of patients pathological acid exposure was present for just one or two nights during the 96-hour recording (21 (36.2%) and 17 (29.3%), respectively).

Night-to-night diagnostic variability of AET

Figures 2a,b show the esophageal acid exposure and the proportion of patients with a pathological supine nighttime acid exposure for the total study population for each day and night separately. There was no overall change in supine nocturnal acid exposure over time (all $P > 0.1$). Night-to-night variance in esophageal acid exposure, reflected by the coefficient of variation, was high (median 94% (IQR 0-144)) and significantly higher than variance in diurnal acid exposure (58% (IQR 32-88), $P < 0.001$). Variance in supine nocturnal acid exposure values compared to the 96-hour average, reduced with increasing length of recording, from 73% (IQR 0-100) in the first 24 hours, to 40% (IQR 0-75) and 13% (IQR 0-29) after 48 and 72 hours respectively, $P < 0.001$). The proportion of patients with a pathological acid exposure for all nights was significantly lower than the proportion of patients with a pathological acid exposure based on worst-night analysis 9/105 (8.6%) versus 63/105 (60.0%), respectively, ($P < 0.001$). Forty-one (39.0%) patients had a consistent diagnosis for all four nights, whereas

Table 1. Demographic and clinical characteristics of included patients stratified for the presence of nocturnal reflux symptoms

	Patients with nocturnal symptoms (*n* = 86), *n* (%)	Patients without nocturnal symptoms (*n* = 19), *n* (%)	P value
Demography			
Sex			
Male	37 (43.0)	3 (15.8)	**0.027**
Female	49 (57.0)	16 (84.2)	
Age, mean ± SD	45.9 ± 13.9	48.6 ± 16.6	0.400
Symptoms at presentation			
Heartburn	76 (88.4)	13 (68.4)	**0.029**
Regurgitation	59 (68.6)	10 (52.6)	0.184
Chest pain	31 (36.0)	2 (10.5)	**0.030**
Cough	24 (36.8)	7 (36.8)	0.440
Belching	22 (25.6)	4 (21.1)	0.679
Dysphagia	19 (22.1)	5 (26.3)	0.692
Throat pain	14 (16.3)	3 (15.8)	0.958
Hoarseness	6 (7.0)	2 (10.5)	0.598
Medical history			
Gastrointestinal comorbidities[a]	5 (5.8)	2 (10.5)	0.608
PPI-use	62 (72.1)	12 (63.2)	0.579
Endoscopic findings			
Gastritis	16 (18.6)	3 (15.8)	1.000
Schatzki ring	8 (9.3)	0 (0.0)	0.345
Reflux esophagitis	18 (20.9)	2 (10.5)	0.296
Grade A	10	2	
Grade B	8	0	
pH study findings			
Nocturnal acid exposure, median (IQR)	2.3 (0.2-5.6)	0 (0-1.5)	**0.002**
Number of nocturnal reflux episodes, median (IQR)	6 (1-12)	1 (0-6)	**0.008**
Pathological nocturnal acid exposure (>1.5%)	48 (55.8)	5 (26.3)	**0.020**
At least 1 nocturnal reflux episode	74 (86.0)	10 (52.2)	**0.001**

IQR interquartile range; *n*, number of patients; PPI, proton pump inhibitor; SD, standard deviation.

[a] Inflammatory bowel disease (*n* = 4), coeliac disease (*n* = 1), eosinophilic enterocolitis (*n* = 1), superior mesenteric artery (SMA) syndrome (*n* = 1).

Bold values denote statistical significance at the P < 0.05 level.

the vast majority would end up with different diagnoses when the nights were to be assessed separately (**Figure 3a**). A diagnosis consistent with that of the 96-hour "gold standard" was present in 83 (79.0%), 91 (86.7%), and 98 (93.3%) patients for 24-, 48-, and 72-hour test periods, respectively, with a significant improvement in diagnostic consistency with duration of pH recording (P < 0.001) (**Figure 3b**).

Night-to-night variability of symptom association

A median of 18 (IQR 10-61) typical reflux symptoms were recorded per patient during the 96-hour reflux measurement period. Eight (7.6%) patients remained entirely symptom-free during the prolonged monitoring period. Combining all typical reflux symptoms recorded during the wireless pH study, 36 of the 105 (34.3%) patients had a positive SI overall. As expected, the frequency of nocturnal symptoms was significantly lower compared to the number of diurnal symptoms (P < 0.001). **Figure 2c** presents the proportion of patients with SI > 50% f or each day and night separately. There was no overall change in symptom frequency and association over time (both P > 0.5). Worst-night analysis showed a positive SI in 31 of the 105 (29.5%) patients. The frequency of symptoms during the nights was low (median 2 (0-6)) and varied substantially. In just one patient, a positive SI for every night of the 96-hour recording could be calculated. Variance in nocturnal SI compared to the 96-hour average, reduced with the increasing length of recording (P < 0.001). A diagnosis consistent with that of the 96-hour "gold standard" was present in 35/44 (79.5%), 48/56 (85.7%) and 62/64 (96.9%) patients for 24-, 48-and 72-hour test periods, respectively (**Figure 3b**). However, the increase in the diagnostic agreement was not statistically significant (P > 0.5).

Added diagnostic yield of prolonged pH monitoring

The diagnostic yield and parameters of diagnostic performance for the detection of pathological supine nocturnal acid exposure were calculated for the first 24-, 48-, 72-hours and worst night and compared to the complete four-night recording as "gold standard" (**Table 2**). The proportion of patients with a pathological supine nighttime acid exposure during the first night (24 hours) was significantly lower than the proportion of patients diagnosed based upon the complete 96-hour recording (32.4% vs 50.5% P < 0.001). If this study population had undergone only one night of pH monitoring, 19 (18.1%) patients would have been missed. If the first two or three nights were taken into account, the diagnostic yield increased to 40.0% and 45.7%; and 11 and 5 patients would have been missed, respectively. The negative predictive value of a reflux-free first night was 72.1%. The diagnostic yield, sensitivity, specificity and positive predictive values all increased with the duration of the pH study. Worst night analysis resulted in 10 more pathological supine nighttime acid exposure diagnoses compared to the gold standard and had the highest sensitivity, but lowest specificity for the detection of pathological supine nighttime acid exposure.

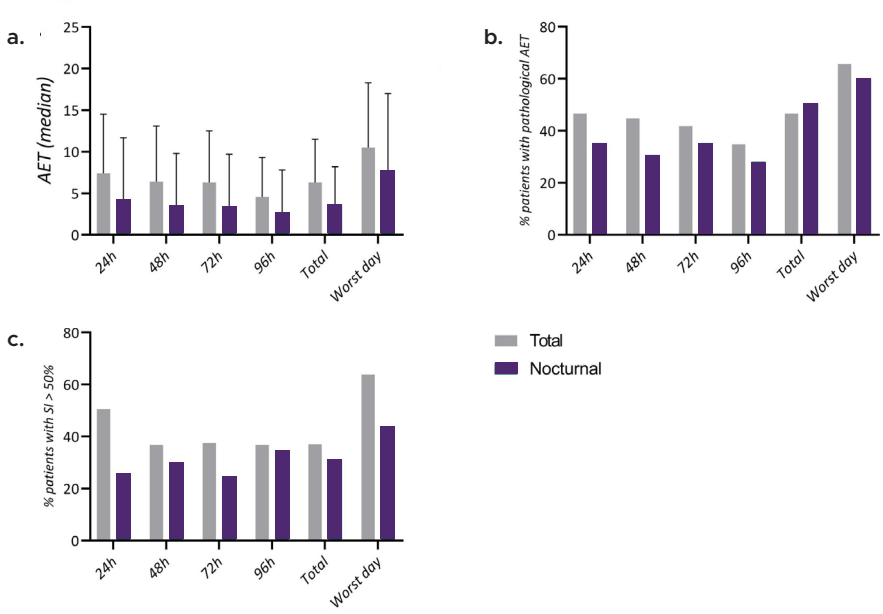

Figure 2. a, Median esophageal acid exposure time; b, the proportion of patients with a pathological supine nocturnal acid exposure; c, the proportion of patients with SI > 50% for each day and night separately

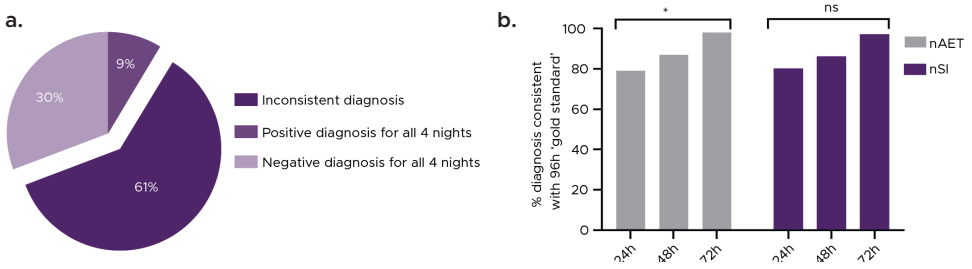

Figure 3. a, Diagnostic agreement (nocturnal acid exposure >1.5%) between the different nights; b, diagnostic consistency between the first 24-, 48- and 72 h with the 96-h "gold standard" for pathological supine nocturnal acid exposure (nAET >1.5%) and symptom index (nSI >50%).

Characteristics of subjects with pathological supine nighttime acid exposure

Patients were stratified for the presence of pathological supine nighttime acid exposure. The presence of cough and reflux esophagitis was more frequently found in patients with abnormal supine nighttime acid exposure ($P < 0.05$). The median time interval from the last meal until the supine period was 2 hours and 41 minutes (IQR 1:39-3:23) but there was no difference in length between the two groups ($P > 0.060$). To further explore predictive factors for nocturnal reflux, we performed a logistic regression analysis with pathological supine nocturnal acid exposure as a dependent variable (**Table 3**). In accordance with the sub-analysis, univariate logistic regression identified the symptoms of coughing, endoscopic reflux esophagitis and presence of pathological daytime acid exposure as predictive factors for nocturnal reflux diagnosis (all $P < 0.05$). Subsequently, in multivariate logistic regression modeling, only the presence of endoscopic reflux esophagitis (OR 3.98; 95% CI 1.15-13.81), $P < 0.05$) was identified as an independent predictor. Of the 53 patients with a pathological supine nocturnal supine acid exposure, 26 (49.1%) had a normal upright acid exposure while in 50.1% an increased bi-positional acid exposure was observed. In patients with pure supine reflux and with bi-positional reflux, the occurrence of reflux was spread more evenly throughout the night and the acid clearance time was longer, compared to the groups of patients with a normal supine nocturnal acid exposure (both $P < 0.001$).

Determinants of supine nocturnal reflux perception

To further assess the characteristics of supine nocturnal reflux, we manually examined a total of 917 supine nocturnal acidic reflux events, of which 857 occurred in the first 8 hours of the supine nocturnal period. The number of reflux episodes was highest in the first hours and significantly decreased thereafter ($P < 0.015$) (**Figure 4**). The occurrence of early reflux was not associated with shorter meal-bedtime interval ($P > 0.05$). Finally, we wanted to look for specific determinants of supine nocturnal reflux perception. In **Table 4**, the characteristics of the reflux episodes which were associated with symptoms were compared with those which were not. In total, 107 reflux episodes were followed by a symptom within 2 minutes, while 810 reflux episodes were not. The nadir pH was significantly lower in the symptom-associated reflux episodes ($P < 0.001$). In addition, we found that the acid clearance time was significantly longer in the symptom-associated reflux episodes compared with the non-associated episodes ($P = 0.02$). No significant differences were found for the baseline pH and the magnitude of the pH drop.

Table 2. Diagnostic performance for the detection of supine nocturnal reflux of the first night, first two nights, first three nights and the worst night compared to the gold standard (complete 96 h recording)

Characteristic	Diagnostic yield[a] *n/N*	Patient missed, *n*	Sensitivity	Specificity	Accuracy[b]	PPV	NPV
96 h (4 nights) "gold standard"	53/105	0	-	-	-	-	-
72h (3 nights)	48/105	5	90.6 (79.3-96.9)	96.2 (86.8-99.5)	93.3 (86.8-97.3)	96.0 (86.0-98.9)	90.9 (81.3-95.9)
48 h (2 nights)	42/105	11	79.3 (65.9-89.2)	94.2 (84.1-98.8)	86.7 (78.6-92.5)	93.3 (2.2-97.7)	81.7 (72.4-88.3)
24 h (1 night)	34/105	19	64.2 (49.8-76.9)	94.2 (84.1-98.8)	79.1 (70.0-86.4)	91.9 (78.8-97.2)	72.1 (64.1-78.8)
Worst night	63/105	0	100.0 (93.3-100.0)	80.8 (67.5-90.4)	90.5 (83.2-95.3)	84.1 (75.2-90.2)	100.00%

Values are presented as percentages with 95% confidence interval, CI, confidence interval; *n*, number of identified supine nocturnal GERD cases; *N*, number of the study sample; NPV, negative predictive values; PPV, positive predictive value.

[a]The diagnostic yield was defined as the proportion of patients in whom prolonged pH monitoring yielded a pathological nighttime acid exposure out of the total number of patients analyzed.

[b]Overall diagnostic accuracy, expressed as a proportion of correctly classified subjects (true positives and true negatives) amongst all subjects was calculated.

Table 3. Logistic regression analysis for identifying predictive factors for pathological supine nighttime acid exposure

	Univariate model			Multivariate model		
Possible risk factor	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Age	1.01	0.98-1.04	0.437			
Gender						
Female	0.54	0.23-1.23	0.128			
Male	Ref.					
Symptoms of heartburn						
Present	1.83	0.61-5.53	0.279			
Absent	Ref.					
Symptoms of chest pain						
Present	2.47	1.00-6.09	0.070			
Absent	Ref.					
Symptoms of regurgitation						
Present	2.26	0.97-5.27	0.088			
Absent	Ref.					
Symptoms of coughing						
Present	0.42	0.18-1.00	**0.049**	0.43	0.17-1.10	0.077
Absent	Ref.					
Endoscopic reflux esophagitis						
Present	7.52	1.51-16.31	**0.006**	3.98	1.15-13.81	**0.029**
Absent	Ref.					
Night-meal interval						
Present	1.00	1.00-1.00	0.058			
Absent						
Pathological daytime acid exposure						
Present	3.12	1.36-7.12	**0.007**	2.33	0.96-5.66	0.063
Absent	Ref.					

CI, confidence interval; OR, odds ratio.
Bold values denote statistical significance at the P < 0.05 level.

Table 4. Characteristics of supine nocturnal reflux episodes stratified for the presence of symptom association

Possible risk factor	Associated reflux episodes (*n* = 107)	Non-associated reflux episodes (*n* = 810)	P value
Acid clearance time (s)	240 (76-912)	133 (57-233)	**0.019**
Baseline pH	6.1 (5.6-7.2)	6.6 (5.9-6.9)	0.261
Nadir pH	2.3 (1.7-2.6)	2.8 (2.4-3.1)	**<0.001**
pH drop	4.0 (3.1-4.9)	3.8 (3.1-4.2)	0.090

N, number of patients; s, seconds.
Bold values denote statistical significance at the P < 0.05 level.

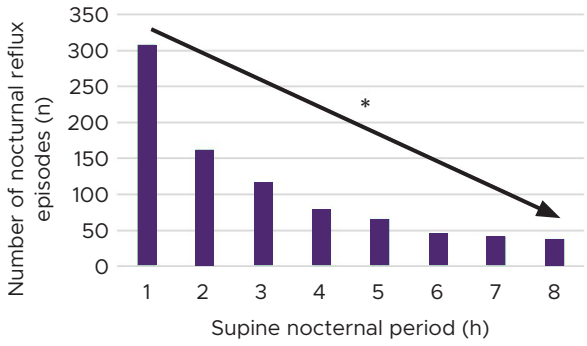

Figure 4. Total number of reflux episodes per hour. The incidence of nocturnal reflux episodes was highest in the first hour of the nocturnal period and decreased thereafter *P < 0.015

DISCUSSION

Nocturnal reflux symptoms are common, however, their etiology and underlying mechanisms are less well studied and remain incompletely understood. Therefore, the appropriate diagnostic and therapeutic strategy to tackle nocturnal reflux might very well differ from standard management of daytime reflux symptoms. For example, it is well known that proton-pump inhibitor (PPIs) have less efficacy for nighttime reflux symptoms compared to daytime symptoms.[17] This is the first study that specifically focused on supine nocturnal reflux and nighttime symptoms using prolonged wireless pH monitoring. We demonstrated that just one or two nights with supine nocturnal reflux may cause bothersome nighttime symptoms. We showed that variance, and in particular, night-to-night variability in wireless pH monitoring is high. As a result, increasing the duration of a pH study from 24 to 72 hours or 96 hours, progressively improved the diagnostic yield and diagnostic accuracy for nocturnal reflux diagnosis. The infrequent occurrence of reflux in the night in combination with high night-to-night variability, can lead to missed (false-negative) diagnoses when based upon 24-hour

testing. This study suggests that prolonged pH monitoring is preferred over a standard 24-hour pH study in the assessment of patients that report nocturnal reflux symptoms.

This study confirms that objective evidence of reflux at night is commonly found in those who complain of nighttime reflux symptoms. Of the group of patients that explicitly reported nighttime symptoms, 67% had pathological nocturnal acid exposure in at least one night. However, in most patients (65%), acid exposure was abnormal in just one or two nights of the total 96-hour recording. This implies that even the sporadic occurrence of reflux at night can lead to bothersome symptoms; however, due to its high variability, nocturnal reflux is easily missed if recordings consist of just one night. Previous studies evaluating pH test reproducibility already showed that the variability for AET and GERD diagnosis is high.[7,18] We showed a similarly high variance for the occurrence of reflux. The night-to-night variance was even higher than the diurnal variance. By extending the recording time of the pH test, there was improved detection of abnormal acid exposure and increased sensitivity for the diagnosis of nocturnal reflux. Of note, repeating or extending the duration of any diagnostic test, increases the probability of observing a positive test result, both true-positives and false-positives. Although we did not observe this effect in our data (probably as a result of the used 96 hours result as "gold standard"), it is important to bear in mind that an increased sensitivity might come at the cost of reduced specificity. Nevertheless, in the context of patients with reflux symptoms under evaluation for anti-reflux surgery, increased sensitivity is preferred over an increased specificity, as it is clinically more relevant to "rule out" than "rule in" in these cases.

The benefit of prolonged recording for the purpose of the symptom-reflux association is less certain. Although the variance in nocturnal symptom association did reduce with increasing length of recording, we did not find any improvement in diagnostic yield. This is in contrast to previous studies.[18,19] Of note, symptom reporting is not likely to be comparable to the daytime as, by its very nature, patients are commonly asleep. This consequently impairs the calculation of symptom association scores and likely explains the lack of added diagnostic value of prolonged recording for nocturnal symptom association in this study.

The finding of a high number of reflux episodes at the beginning of the nocturnal period is consistent with previous studies.[20] Interestingly, in patients with pure supine or bi-positional reflux, reflux episodes were spread more evenly throughout the night and the acid clearance time was longer, whereas reflux in patients with a normal supine nocturnal acid exposure mainly occurred in the first hours of the night and are shorter in general. Although it has been suggested that the consumption of a late evening meal evokes the occurrence of early nocturnal reflux,[21] we did not find a significant relation between the length of meal-night interval with the occurrence of early reflux, suggesting that early nighttime reflux is not simply a postprandial phenomenon, but that other factors most likely play a role. In healthy subjects,

nocturnal acid reflux is very rare and occurs primarily during transient lower esophageal sphincter relaxations (TLESRs).[9] TLESRs do only occur during awake periods or transient arousals from sleep, which might explain that in patients with physiological nocturnal acid exposure, reflux occurs mainly through TLESRs at the beginning of the recumbent period, while still being awake. In contrast, reflux as a result of poor motility or hypotensive LES, which is more common in (bi-positional and supine) reflux patients,[22] will occur more consistently throughout the night.

We assessed why some reflux episodes trigger nocturnal symptoms and others do not. Not surprisingly, nightly reflux episodes with a lower nadir pH or longer acid clearance time were more prone to evoke symptoms. This supports the hypothesis that despite the infrequent occurrence of nighttime reflux, one acidic reflux episode with long acid contact time can still cause bothersome nocturnal symptoms. Previous studies that assessed reflux episodes, in general, have made clear that the acidity of the refluxate is an important determinant of perception of typical reflux symptoms.[23] In contrast to these studies, we did not find a significant difference when evaluating the size of the pH drop.

Some limitations must be acknowledged. First, in the absence of more advanced techniques such as sleep polysomnography, the difference between the recumbent-awake and the recumbent-asleep period and consequently, the effect of sleep itself on reflux was not taken into account. In line with this, we equated the patient-reported supine period as “nocturnal” or “nighttime,” which potentially could have introduced bias. Second, normative nocturnal reflux data is currently lacking for wireless pH systems. Therefore, we had to rely on catheter-based studies to define our diagnostic threshold for pathological nocturnal acid exposure. Last, Bravo capsule placement was performed under sedation, which might have affected esophageal motility and potentially nocturnal reflux on the first recording day. However, the AET and the number of reflux episodes recorded on the first day and night did not significantly differ compared to any of the other days and nights.

CONCLUSION

We demonstrated that the majority of patients with nocturnal reflux symptoms had pathological supine nighttime acid exposure in at least one night of the prolonged pH recording. An observed high night-to-night variability in acid exposure and infrequent symptom reporting reduces the clinical value and diagnostic yield of pH monitoring limited to 24 hours. Prolonged reflux monitoring is a more appropriate diagnostic tool for patients with nocturnal reflux symptoms.

AUTHOR CONTRIBUTIONS

RON, RS and AB played a role in planning of the study. RON, RS and AB had a role in conducting the study. RS and HAR were involved in the acquisition of data. RON, RS, HAR, RR, TW, JS, JO and AB had a role in collecting and/or interpreting data. RON played a role in drafting the manuscript. RS, JS, JO, RR, TW, AS and AB played a role in reviewing and revising the manuscript for important intellectual content. All authors had access to the study data and reviewed and approved the final manuscript.

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The effect of STW5 (Iberogast) on reflux symptoms in dyspeptic patients: a double-blind randomized placebo-controlled crossover trial

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Submitted

ABSTRACT

Background

It has been suggested that STW5 (Iberogast®) reduces heartburn symptoms in patients with functional dyspepsia, but underlying mechanisms of action are unclear. The aim of this study was to investigate whether STW5 affects esophageal sensitivity or esophageal motility, thereby reducing occurrence and perception of reflux events.

Methods

We performed a double-blind, randomized, placebo-controlled, crossover trial in patients with functional dyspepsia (Rome IV) and reflux symptoms. Patients were randomly assigned (1:1) to four weeks of STW5 treatment followed by four weeks of placebo treatment, or assigned to the opposite treatment order. After 4 weeks of treatment with either placebo or STW5, patients were studied with an esophageal acid perfusion test and ambulatory 24h pH-impedance monitoring. Our primary outcome was the Reflux Disease Questionnaire (RDQ) score. Secondary outcomes included esophageal sensitivity scores, total acid exposure and the number of reflux events.

Results

A total of 18 patients (7 men, median age 54, range (19-76)), were included in the study. Although we found no statistical difference in the total RDQ score 2.33 (0.25-4.33) vs 2.67 (1.17-4.00), P = 0.347, 'GERD' and 'regurgitation' subscale scores were lower after STW5 treatment compared to placebo (P = 0.049 and P = 0.007). There was no statistical difference in number of reflux events, acid exposure time and acid sensitivity scores between STW5 and placebo. In a subgroup analysis of patients with pH-metry confirmed GERD, treatment with STW5 significantly reduced the total number of acidic reflux events (P = 0.028). Moreover, in patients with reflux esophagitis, the median lag time to acid perception increased after STW5 treatment (P = 0.042). We observed no relevant adverse events.

Conclusions

We found some indications pointing towards a beneficial effect of STW5 on reflux symptoms in dyspeptic patients, with reduction of esophageal hypersensitivity as a potential underlying mechanism. Our findings will have to be confirmed in larger studies.

INTRODUCTION

Dyspeptic symptoms are one of the most prevalent reasons for consultation of a general practitioner and frequently lead to referral to a gastroenterologist.[1] Although dyspeptic symptoms can have organic causes such as gastric malignancies or peptic ulcer disease, in most situations, an organic cause cannot be found and the diagnosis of functional dyspepsia is made. The symptom presentation in functional dyspepsia differs greatly. Most patients describe epigastric pain as the predominant symptom, often associated with other complaints including epigastric fullness, nausea, bloating, or heartburn.[2] The pathophysiology of functional dyspepsia is multifactorial; impaired gastric emptying, visceral hypersensitivity and helicobacter pylori infection all play a role.[3] As a result, targeted therapy in these patients is complex and often directed by the type of clinical symptoms. Although acid-suppressive drugs, prokinetics, Helicobacter pylori eradication and psychotropic drugs have all been shown to be effective, the effect of these therapies is only modest, and in the majority of patients, the symptoms persist.[4] In line with this, functional dyspepsia with heartburn is often treated with a proton pump inhibitor (PPI), although its effect is limited.[5] It has been suggested that the explanation for the poor therapeutic response in these patients is that pharmacological therapies only tackle one aspect of functional dyspepsia, whereas it is a multifactorial disorder. A post-hoc analysis of a randomized controlled trial showed that STW5 (Iberogast®), an herbal preparation that has proven efficiency in placebo controlled trials for functional gastrointestinal disorders such as functional dyspepsia (FD) and irritable bowel syndrome (IBS), effectively reduced heartburn in patients with functional dyspepsia.[6] However, the mechanism of action of STW5 in reduction of reflux symptoms is unknown. It has been demonstrated that STW5 affects gastric motility in healthy controls and in an in-vitro model,[7,8] which could theoretically result in a reduced number of reflux events.[9] Another study showed that STW5 can decrease afferent sensitivity in the small intestine, and therefore STW5 could potentially also have an effect on esophageal visceroperception.[10] Given that the effect of PPI in functional dyspepsia with reflux symptoms is limited and that there are few alternatives, there is a demand for new multi-target therapies in functional dyspepsia. Therefore, we aimed to study the effect of STW5 on patients with functional dyspepsia and heartburn and its underlying working mechanisms, in particular its effect on reflux symptoms, incidence of reflux episodes and esophageal sensitivity.

METHODS

Study design

We performed a single-center, double-blind, randomized placebo-controlled, crossover trial in dyspeptic patients with reflux symptoms between June 2015 and April 2021 (**Figure 1**). Patients were randomly assigned in a double-blind fashion in a 1:1 ratio to either one of the two treatment blocks. Randomization was conducted by the hospital trial pharmacist. One group of patients received 4 weeks of STW5 (20 drops three times daily), followed by

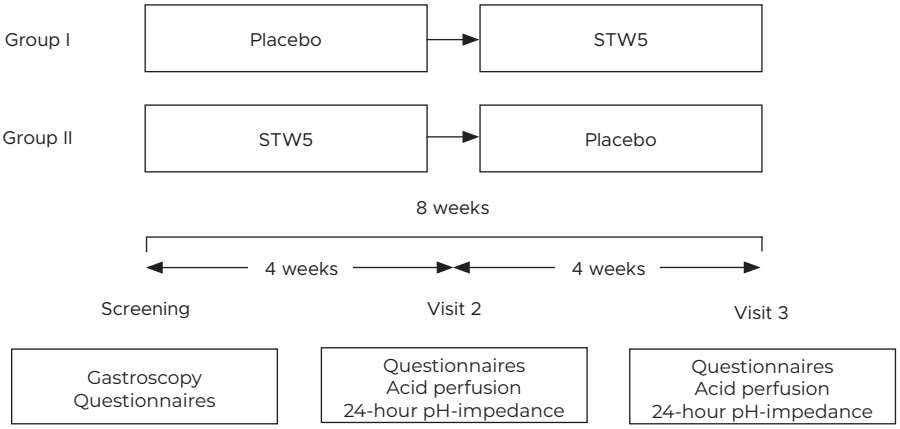

Figure 1. Schematic study outline

a second 4-week period in which patients received placebo. The patients assigned to the other study arm, started with placebo for 4 weeks, followed by STW5 for 4 weeks. On the last day of the 4 week treatment period, patients underwent an esophageal acid perfusion test to assess esophageal sensitivity to acid. Subsequently, patients went home with an ambulatory pH-impedance recording device. Gastroesophageal reflux events and acid exposure time were monitored for 24 hours. Gastric acid suppressants or medication that potentially affected esophageal motility were discontinued 7 days before inclusion. Reflux and dyspeptic symptoms were evaluated at the end of each of the 4-week treatment periods. The study was conducted according to the principles of the Declaration of Helsinki, complied with Good Clinical Practice (GCP) and the Dutch Act on Medical Research Involving Human Subjects (WMO). Written informed consent was obtained from all patients before study participation. The Clinical Research Unit of the Amsterdam University Medical Center (UMC) monitored the study. The study was prospectively registered in the Dutch trial registry (Trial NL6112 NTR6252, trialregister.nl).

Patient selection

We included adult patients with a history of dyspepsia, according to the ROME IV criteria.[11] who, in addition, had symptoms of heartburn. Patients were excluded if they had undergone esophageal or gastric surgery, a history of other gastroesophageal diseases including Barrett's esophagus and gastrointestinal malignancies, or used medication with a potential effect on gastrointestinal motility, secretion or sensitivity that could not be stopped. If not previously performed, an upper endoscopy and abdominal ultrasonography were performed prior to inclusion to rule out other upper gastrointestinal disorders that could explain the symptoms.

Study medication

Verum and placebo were provided by Steigerwald Arzneimittel GmbH, Bayer Consumer Health. STW5 consists of hydroethanolic herbal extracts from bitter candy tuft, peppermint leaf, chamomile flower, liquorice root, Angelica root, caraway fruit, milk thistle fruit, Melissa leaf and greater celandine herb. A placebo of similar appearance and taste was used in order to ensure that the patients were not able to discriminate between active treatment and placebo (Coloring agents: yellow orange E 110, quinolone yellow E 104 and brilliant black E 151. Flavoring substances: Herbage aroma Sym 202848 and Liquorice aroma Sym 202850). Study medication was packaged in labelled white boxes and these were stored and dispensed on a patient-named basis by the Amsterdam UMC Trial Pharmacy conform Good Clinical Practice (GCP) guidelines. In all previous clinical studies, STW5 was administered as 20 drops three times daily in a small amount of liquid, taken orally before or during meals. For this study, the same dosage and route of administration were applied.

Study procedures

Esophageal manometry and acid perfusion (Bernstein) test

A water-perfused manometry catheter fitted with 7 side holes at 5-cm intervals and an additional side-hole for the acid perfusion was introduced transnasally and positioned to measure pressures from hypopharynx to stomach. Following a standardized protocol, patients were placed in supine position (20˚) and received 10 boluses of 5 mL water at intervals of 20 s. Before and after the wet swallows, a period of 30 s without swallows was included for baseline measures. After an adaptation period of 15 minutes, saline was infused into the esophagus for 5 minutes, followed by infusion of 0.1 M of hydrochloric acid for a duration of 15 minutes or until the patient reported heartburn that was intense enough to induce discomfort or pain. The perfusion test was terminated before the maximum duration of 15 minutes in those who reported pain. Patients were blinded for the infused solution. Both saline and hydrochloric acid were instilled at a rate of 8 mL/min, as controlled by an automatic pump (IVAC 560 Volumetric Pump; Rhys Int. Ltd, Bolton, UK). Subjects were asked to report all esophageal or thoracic sensations during the acid perfusion test and to rate them on a VAS scale.

Ambulatory 24-hour pH-impedance monitoring

After the manometry catheter was removed, a 24-hour esophageal pH-impedance study was carried out using a combined pH-impedance catheter assembly (Unisensor AG, Attikon, Switzerland). The catheter contained six impedance recording segments which were located at 2–4, 4–6, 6–8, 8–10, 14–16 and 16–18 cm above the upper border of the manometrically localized lower esophageal sphincter (LES) and one ion-sensitive field-effect transistor pH electrode which was placed 5 cm above the upper border of the LES. The impedance and pH signals were stored on a digital data logger (Ohmega, MMS, Enschede, the Netherlands), using a sampling frequency of 50 Hz and 1 Hz, respectively. Patients were instructed to press the event marker button on the pH data logger whenever they were experiencing symptoms.

During the 24-hour monitoring period, the patients consumed 3 meals and 4 beverages at fixed times and kept a diary of symptoms, meal periods and the period spent in the supine position.

Symptom questionnaires

Prior to inclusion all patients underwent a complete symptom assessment. Recorded data included duration and type of symptoms, demographics, medication use, intoxications, and medical history. Reflux and dyspeptic symptoms were assessed using the Reflux Disease Questionnaire (RDQ) and the Short Form Nepean Dyspepsia Index Questionnaire (SF-NDI)[12,13] at the end of each of the 4-week treatment periods. The RDQ is a 12-item questionnaire assessing the current severity and frequency of 3 GERD-related symptom domains (heartburn, regurgitation and epigastric pain). Each domain is assessed by four questions, all rated on a 5-point Likert scale. The mean of all three dimensions gives a total score ranging from 0 to 5. The specific GERD dimension is determined by the mean of the dimensions heartburn and regurgitation.

Data analysis

Outcome measures

The predefined primary outcome of the study was the total RDQ score. Secondary outcomes included RDQ subscores, esophageal sensitivity and motility parameters, number of reflux events and acid exposure recorded during the 24-h pH-impedance study and dyspepsia symptom scores.

Manometry and Bernstein test

The time interval between the start of acid infusion to initial perception, discomfort, pain and the maximum VAS score during acid perfusion were noted. The perfusion sensitivity score (PSS) was calculated as (total acid perfusion time – lag time to discomfort) × maximum VAS.[14] Esophageal motility was evaluated according to the classification of Spechler and Castell for conventional manometry.[15]

Ambulatory 24-h pH-impedance monitoring

Ambulatory 24-hour pH-impedance tracings were analyzed manually by two investigators independently. Gastroesophageal reflux events were detected using the impedance tracings and classified into acidic and weakly acidic reflux episodes. Total acid exposure time, defined as the percentage of time with pH < 4, was assessed in the upright and supine position. The correlation between reflux symptoms and reflux events was analyzed using the symptom index (SI) and symptom association probability (SAP), in which a positive correlation was defined as occurrence of a symptom episode within 2 min from the start of a reflux event.

Statistical analysis

Sample size calculation

The sample size calculation was based on a previous study which made a post-hoc analysis of patients of three placebo-controlled trials in which the effect of STW5 on functional dyspepsia was investigated using the validated gastrointestinal symptom score (GIS).[6] A total of 135 patients in that report had moderate reflux symptoms, patients with severe reflux symptoms were not included. This post-hoc study found a mean decrease in reflux symptom score of 1.06 in the active treatment group compared to 0.70 in the placebo group with a P value of 0.0004. The standard deviation calculated from this information is approximately 0.57. Using a paired 2-sided T-test with a significance level of 5% and a power of 80%, the sample size required for our study was therefore 22 subjects. However, since patients with more severe reflux symptoms were not included, we estimated that this sample size is slightly overestimated since patients who have more reflux symptoms are more likely to show a larger effect of the treatment. Therefore we decided to use a standard deviation of 0.5 which resulted in a required sample size of 18 subjects.

Endpoint analysis

Descriptive statistics were presented as percentage for categorical data and as mean with standard deviation or median with range for continuous variables. Analysis was performed using the paired Student t-test for parametric data and the Wilcoxon signed rank test for non-parametric data. The log-rank test was used to compare lag times to perception, discomfort and pain. A P value of <0.05 was considered significant. SPSS statistics (version 26; SPSS, Chicago, Illinois, USA) was used for statistical analysis.

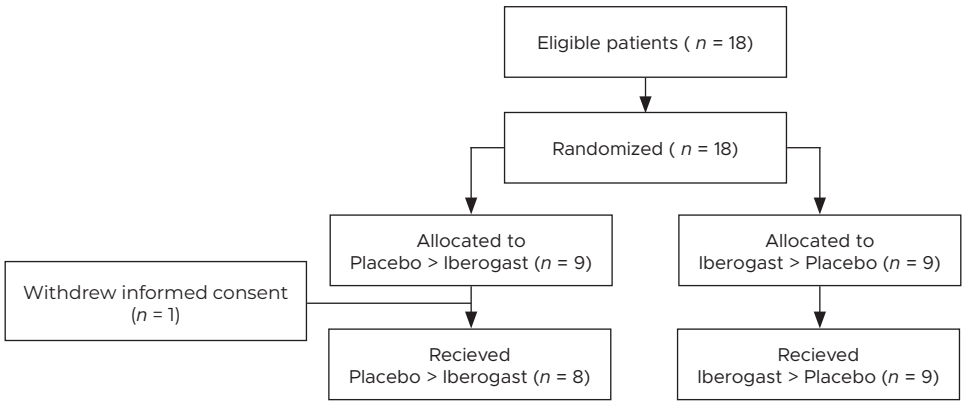

Figure 2. Participant flow diagram

RESULTS

Patient characteristics

A total of 18 patients (7 men, median age 54 (range 19-76), and body mass index (BMI) of 26 (19-39)) were included in the study. Nine patients were randomized to receive placebo first, the other nine patients received STW5 first (**Figure 2**). One patient withdrew informed consent before the first day of study tests. All patients described a history of dyspepsia according to the Rome IV criteria and reported symptoms of heartburn with a median duration of 17 (2-192) months. The main patient characteristics and demographics are presented in **Table 1**. Upper endoscopy was performed in all patients prior to inclusion. A hiatal hernia was seen in 6 (33.3%) patients and 8 (44.4%) patients were diagnosed with reflux esophagitis; 6 patients grade A, one patient grade B and in one patient the grade was not specified. The majority (88.9%) of patients used medication prior to inclusion to reduce reflux symptoms, proton pump inhibitors being the most frequently used. Ten (55.6%) patients were classified as overweight (BMI > 25).

Primary outcome: reflux symptoms

The total RDQ score (median, IQR) after four weeks of placebo treatment was 2.67 (1.17-4.00) versus 2.33 (0.25-4.33) after four weeks of STW5 treatment. This difference was not statistically significant (P = 0.347). However, there was a significant decrease in the subscales 'GERD' (2.75 (0.00-3.88) vs 1.75 (0.00-4.25), P = 0.049) and 'regurgitation' (2.50 (0.00-4.25) vs 1.75 (0.00-4.00), P = 0.007) when STW5 was used. The heartburn and dyspepsia subscales did not differ between the two treatment periods (P = 0.991 and P = 0.359), as shown in **Figure 3**.

Secondary outcomes

Esophageal acid perfusion test

Most patients developed symptoms during esophageal acid perfusion, both after 4 weeks of placebo treatment (88.2%), and after four weeks of STW5 treatment (88.2%). Although the median lag times until first perception, discomfort and pain were higher after STW5 treatment than after placebo (3, 8 and 8 min vs 1, 6 and 4 min), these differences were not statistically significant (**Table 2**) Maximum VAS pain scores during STW5 and placebo treatment were similar (5.7 (2.8-9.6) vs 5.7 (1.4-8.9) P = 0.201). Perfusion sensitivity scores after treatment with STW5 and after placebo were not significantly different (14.8 (0-107.8 vs. 17.4 (0-115.2), P = 0.594).

Ambulatory 24-hour pH-impedance monitoring

The total acid exposure time after 4 weeks of STW5 was 4.0% (0.8-13.3) compared to 5.9% (0.2-19.3) after placebo treatment, however this difference was not statistically significant (P = 0.997) (**Table 3**). Likewise, there were no differences in the incidences of reflux episodes (total, acidic and weakly acidic) after treatment with STW5 when compared with the incidences after placebo treatment (P values 0.623, 0.820 and 0.777, respectively).

Table 1. Baseline characteristics of included patients (*n* = 18)

	n	(%)	Median (range)
Demography			
Sex			
Male	7	38.9	
Female	11	61.1	
Age at inclusion (years)			54 (19-76)
BMI			26 (19-39)
Reflux symptom duration (months)			17 (2-192)
Medication use prior to participation	16	88.9	
Proton pump inhibitors (PPI)	14	77.8	
H2 antagonist	3	16.7	
Antacids	6	33.3	
Endoscopic findings			
Reflux esophagitis	8	44.4	
Grade A	6	75.0	
Grade B	1	12.5	
Not specified	1	12.5	
Hiatal hernia	6	33.3	
Hernia and esophagitis	4	22.2	

BMI, body mass index; *n*, number of patients.

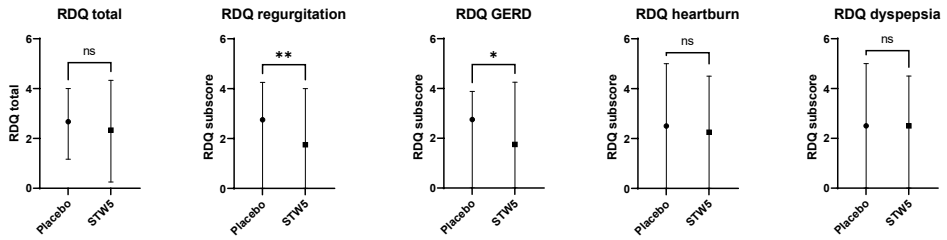

Figure 3. Reflux Disease Questionnaire score (total and dimensions). ** P < 0.01; * P < 0.05.

Table 2. Esophageal acid perfusion (Bernstein) test after four weeks of STW-5 and four weeks of placebo treatment (*N* = 17)

	Placebo			STW5			
	Median	**range**	***N (%)***	**Median**	**range**	***N (%)***	**P value**
Perception occurred			15 (88.2)	3		15 (88.2)	
Time to perception (min)	1	0-10			0-11		0.257
Discomfort occurred			11 (64.7)	8		12 (70.6)	
Time to discomfort (min)	6	1-14			1-14		0.398
Pain occurred			2 (11.8)	8		2 (11.8)	
Time to pain (min)	4	2-6			1-15		*
Maximum VAS	5.7	1.4-8.9		5.7	2.8-9.6		0.201
Perfusion sensitivity score (PSS)	14.8	0-107.8		17.4	0-115.2		0.594

N, number of patients; PSS, perfusion sensitivity score; VAS, visual analogue scale; * not enough events to calculate P value.

Manometry

In one patient esophageal motility was classified as ineffective based on both manometries. Another patient was diagnosed with diffuse esophageal spasm with more than >20% simultaneous contractions based on one of the two manometries. All other patients had normal esophageal peristalsis. As can be seen in **Table 3**, there were no statistically significant differences in distal wave amplitude, LES basal and LES relaxation pressures for the two treatment groups.

Dyspeptic symptoms and Health-related quality of life

No significant difference in health-related quality of life was seen after treatment with STW5 compared with placebo. Likewise, the Short-Form Nepean Dyspepsia Index (SF-NDI) was statistically not different after treatment with STW5 versus placebo (18 (0-30) vs 12 (4-29) P = 0.924). In line with this, no significant difference was seen in the weighted dyspepsia score when comparing placebo 1.60 (0.24-2.87) to STW5 1.78 (0.24-2.96) (P = 0.072).

Subgroup analysis

To evaluate the effect of STW5 on patients with demonstrated reflux disease, two subgroup analyses were performed. First, a subgroup analysis was performed in the 8 patients with an acid exposure >6% during the pH-impedance study after 4 weeks of placebo treatment (**Supplemental Table 1**). Secondly, the 7 patients with endoscopic reflux esophagitis were analyzed separately (**Supplemental Table 2**). In line with the results of the total study population, no statistically significant improvement in median RDQ scores, acid exposure time, maximum VAS score and PSS was observed after STW5 treatment for the two subgroups. However, in the subgroup of patients with a pathological acid exposure, the number of acidic

Table 3. Esophageal pH-impedance and manometry parameters after four weeks of STW5 and four weeks of placebo treatment (*N*=17)

	Placebo			STW5			P
Ambulatory pH-impedance monitoring	**Median**	**range**	***N***	**Median**	**range**	***N***	**value**
Acid exposure time (%)							
Total	5.9	0.2-19.3		4.0	0.8-13.3		0.977
Upright	5.9	0.3-25.6		3.4	0.0-23.2		0.638
Supine	1.5	0.0-14.7		0.2	0.0-27.7		0.280
Total reflux episodes, *n*	41	9-120		45	5-136		0.623
Acidic reflux episodes	28	8-82		31	4-57		0.820
Weakly acidic reflux episodes	11	0-57		9	1-79		0.777
Reflux episodes supine	2	0-23		3	0-37		0.615
Reflux episodes upright	38	5-97		40	1-99		0.756
Manometry							
Lower esophageal sphincter (LES) pressures							
Basal pressure	7	0-26		9	0-25		0.462
Relaxation pressure	4	0-10		3	0-8		0.265
Esophageal motility parameters							
Distal peristaltic wave amplitude	55	32-150		69	19-143		0.959
Gastric pressure	6	0-23		9	0-16		0.324
Classification of esophageal motility *							
Normal motility			15			16	
Ineffective esophageal motility			1			1	
Diffuse esophageal spasm			1			0	

N, number of patients; * classification according to Spechler and Castell[15]

reflux episodes was significantly lower from 52 (17-82) to 33 (4-57) after STW5 treatment (P = 0.028). Moreover, as displayed in **Figure 4**, a significant increase in median lag time until perception to acid from 1.5 (0-10) to 3 (0-11) minutes was observed in patients with reflux esophagitis (P = 0.042).

Adverse events

No serious adverse events occurred during this trial. Worsening of dyspeptic symptoms during placebo treatment led to the termination of the study in one patient. Abdominal pain (*n* = 1) and diarrhea (*n* = 1) were reported during placebo treatment. One patient reported dysphagia during placebo treatment, and one patient during STW5 treatment. However, symptoms resolved after treatment with antacids. During treatment with STW5 one patient

reported loss of appetite and one patient reported nausea which were both mild and resolved spontaneously. Transient symptoms of headache were reported by one patient during STW5 treatment.

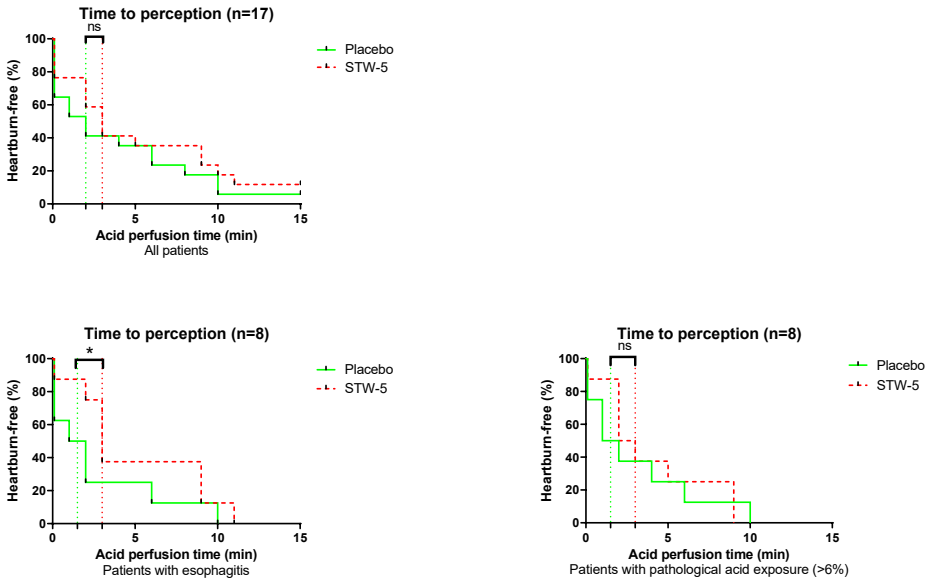

Figure 4. Median lag times until perception to acid in the total study population (*n* = 17), patients with esophagitis (*n* = 8) and patients with pathological acid exposure times, >6% (*n* = 8). * P < 0.05.

DISCUSSION

Dyspeptic symptoms are very common and patients often display a variety of gastrointestinal symptoms, including reflux symptoms such as heartburn and regurgitation. Due to a multifactorial etiology, patients with functional dyspepsia often respond poorly to pharmacological therapy. This randomized controlled trial studied the effect of STW5, a multi-target herbal preparation, on reflux and reflux symptoms in dyspeptic patients, specifically focusing on its potential underlying mechanisms of action. Although we did not find a significant effect in the total RDQ score for STW5 compared to placebo, RDQ subscales 'GERD' and 'regurgitation' were lower after STW5 treatment compared to placebo. In a subgroup analysis of patients with pH-metry confirmed reflux disease, the number of acidic reflux events was lower after treatment with STW5 compared to placebo. Moreover, patients with reflux esophagitis became less sensitive to acid after treatment with STW5. Our findings suggest that STW5 is a safe and potentially effective add-on therapy for reflux symptoms in dyspeptic patients. Nevertheless, the mechanisms underlying these effects remain incompletely understood, as we found no

statistically significant differences for acid perfusion sensitivity scores and esophageal motility after 4 weeks of STW5 treatment compared to placebo.

Although our primary endpoint, the total RDQ score, was 2.3 after 4 weeks of STW5, compared to 2.7 after 4 weeks of placebo treatment, we observed no significant difference. In line with this, the difference in total acid exposure after STW5 treatment (from 6% to 4%), was not statistically significant. Although these endpoints all seemed to improve after STW5 treatment, we were not able to objectify a statistically significant effect, which may indicate that either STW5 has no beneficial effect on reflux symptoms, or that our sample size was insufficient to show a significant difference. The finding that the RDQ subscales 'GERD' and 'regurgitation' were lower after STW5 treatment compared to placebo, suggest that STW5 potentially has a favorable effect on reflux symptoms. The reason for the lack of effect in our primary outcome might lie in our sample size calculation, which was based on a post-hoc analysis of dyspeptic patients with heartburn, however by downsizing the standard deviation and using a power of 80%, our sample size calculation possibly was underpowered, leading to a type II error. This might also explain the lack of effect of STW5 on dyspeptic symptoms in this study; after four weeks of treatment with STW5 the SF-NDI dyspepsia score decreased from 18 to 12, which was not statistically significant, while several trials have reported superiority of STW5 over placebo for the relief of dyspeptic symptoms.[16,17] Another factor that might have contributed was our heterogeneous study population. We included patients with functional dyspepsia accompanied by symptoms of heartburn, and did not use pH-metry to confirm presence of GERD prior to inclusion. Instead, we opted for a pragmatic approach and included a typical primary care population, which constitutes the largest subset of patients referred to the gastroenterologist. Nevertheless, a study population of confirmed GERD cases with a higher initial symptom and reflux burden, would probably have increased the treatment effect.

Although herbal drugs have a long history of use in the treatment of dyspeptic symptoms, their underlying working mechanisms are often incompletely understood. Previous in vitro studies have shown that STW5 has a region-specific effect on gastric motility by relaxing the proximal stomach and increasing antrum contractility.[8,18,19] This region-specific effect was also described by Pilichiewicz *et al.*, who studied 29 healthy volunteers and found that STW5 increased proximal gastric volume while increasing antral pressure waves.[7] These findings may suggest a mechanistic rationale for STW5. In contrast to these studies, we specifically evaluated the effect of STW5 on esophageal motility. We observed no differences in distal wave amplitude, LES basal and relaxation pressures, which suggests that STW5 has no effect on esophageal motility. However, acid exposure time decreased from 6 to 4%, without a change in the total number of reflux events, which potentially suggests that acid clearance time was shorter when patients used STW5. This could implicate that reduced volume of refluxed acid, possibly a result of improved gastric emptying, and thus gastric motility, might

underlie the pharmacological effect of STW5. The finding that in patients with pathological acid exposure fewer reflux events were recorded on STW5 than on placebo further supports this hypothesis. Another proposed target of STW5 is esophageal hypersensitivity. Previous experimental animal studies have found that STW5 can decrease afferent sensitivity in the small intestine, which suggests that STW5 may also have an effect on esophageal visceral perception.[10] We investigated this concept by studying esophageal sensitivity to acid using the Bernstein test. The median lag times to symptom perception, discomfort, and pain were higher after treatment with STW5 compared to placebo. Although these differences were not statistically significant, it might suggest a favorable effect of STW5 on esophageal hypersensitivity. Interestingly, in the subgroup of patients with reflux esophagitis, we did find a significant decrease in acid perception after treatment with STW5. Several previous studies have shown that esophageal sensitivity to acid is increased in patients with demonstrated GERD as compared to healthy controls, which might also be the explanation for the significant effect in our subgroup analysis.[20]

The results of this study give some insight in the potential therapeutic targets of STW5. Our study suggests a beneficial effect of STW5 for reflux symptoms in dyspeptic patients. Based on a large body of evidence and over 60 years of experience with STW5 in clinical practice, we know that STW5 has an excellent safety profile. Likewise in our study, STW5 was well-tolerated without any relevant adverse effects. Therefore, STW5 can be considered as an accessible and safe first-line therapeutic option for patients with dyspepsia and reflux symptoms. Some limitations must be acknowledged. As previously mentioned, it is likely that our study was underpowered with a too small study sample, resulting in a non-significant difference in our primary outcome (ie, type II error). Secondly, we specifically focused on esophageal motility, while gastric motility seems to be a more important therapeutic target of STW5. Gastric emptying scintigraphy would have provided more information in this regard. Nevertheless, this is the first study that assessed the effect of STW5 on esophageal motility and hypersensitivity in dyspeptic patients with concomitant reflux symptoms. Although we found some indications pointing towards a beneficial effect of STW5 in this patient group, our findings will have to be confirmed in larger studies.

CONCLUSION

Although we found no statistical difference in the total RDQ score, ‘GERD’ and ‘regurgitation’ subscale scores were lower after STW5 treatment compared to placebo. Moreover, STW5 was well-tolerated without relevant adverse effects. Therefore, STW5 should be considered as a safe, and potentially, effective first-line therapy for reflux symptoms in dyspeptic patients. Our findings point towards a reduction in esophageal hypersensitivity as potential mechanism of action. Nevertheless, future studies should confirm our results and clarify the exact underlying mechanisms through which STW5 acts.

AUTHOR CONTRIBUTIONS

RON, BK, TH, AB and AS played a role in planning of the study. RON, TK, and TH had a role in conducting the study. RON, TK and JO were involved in the acquisition of data. RON, TK and AB had a role in collecting and/or interpreting data. RON and TK played a role in drafting the manuscript. BK, TH, JS, JAS, and AB played a role in reviewing and revising the manuscript for important intellectual content. All authors approved the final draft submitted.

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Subgroup analysis in patients with pathological acid exposure (AET > 6%), *n* = 8

	Placebo			STW5			
Primary outcome	**Median**	**range**	***N***	**Median**	**range**	***N***	**P value**
RDQ	2.29	1.17-3.92		2.29	0.25-4.08		0.233
pH impedance parameters							
Total acid exposure time (%)	10.6	6.3-19.3		8.0	2.2-13.1		0.310
Total reflux episodes, *n*	60	18-120		50	5-136		0.528
Acid reflux episodes, *n*	52	17-82		33	4-57		**0.028**
Weakly acidic reflux episodes, *n*	10	0-57		8	1-79		0.400
Esophageal sensitivity							
Time to perception (min)	1	0-10	7 (87.5%)	3	0-9	8 (100%)	0.528
Time to discomfort (min)	9	3-14	4 (50%)	11	3-13	6 (75%)	0.674
Time to pain (min)	6	6-6	1 (12.5%)	-	-	0 (0%)	-
Perfusion sensitivity score (PSS)	4.5	0-84.0		15.4	0-115.2		0.398
Manometric parameters							
Gastric pressure	7	1-23		11	1-16		0.746
LES basal pressure (mmHg)	8	3-19		9	0-13		0.865
LES relaxation pressure (mmHg)	4	0-8		3	0-7		0.596
LES distal wave amplitude	66	32-121		61	19-129		0.575

AET, acid exposure time; LES, Lower Esophageal Sphincter; RDQ, Reflux Disease Questionnaire.
Bold values denote statistical significance at the P < 0.05 level.

Supplemental Table 2 Subgroup analysis in patients with endoscopic reflux esophagitis, *n* = 8

	Placebo			STW5			
Primary outcome	**Median**	**range**	***N***	**Median**	**range**	***N***	**P value**
RDQ	2.58	1.17-3.92		2.42	0.58-4.08		0.528
pH impedance parameters							
Total acid exposure time (%)	8.0	1.0-19.3		7.1	2.2-12.9		1.000
Total reflux episodes, *n*	45	18-92		52	5-91		0.833
Acid reflux episodes, *n*	33	17-82		37	4-52		0.735
Weakly acidic reflux episodes, *n*	10	1-13		8	1-16		0.666
Esophageal sensitivity							
Time to perception (min)	1	0-10	7 (87.5%)	3	0-11	8 (100%)	**0.042**
Time to discomfort (min)	6	3-14	6 (75%)	12	3-13	6 (75%)	0.068
Time to pain (min)	6	6-6	1 (12.5%)	15	6-15	1 (12.5%)	-
Perfusion sensitivity score (PSS)	33.4	0-84.0		15.4	0-115.2		0.398
Manometric parameters							
Gastric pressure	7	0-14		12	0-13		0.340
LES basal pressure (mmHg)	16	3-26		9	0-16		0.141
LES relaxation pressure (mmHg)	4	0-10		3	0-8		0.112
LES distal wave amplitude	83	32-150		63	19-129		0.263

AET, acid exposure time; LES, Lower Esophageal Sphincter; RDQ, Reflux Disease Questionnaire.
Bold values denote statistical significance at the P < 0.05 level.

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6

The natural course of giant paraesophageal hernia and long-term outcomes following conservative management

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ABSTRACT

Background

Accurate information on the natural course of giant paraesophageal hernia is scarce, challenging therapeutic decisions whether or not to operate.

Aim

We aimed to investigate the long-term outcomes, including hernia-related deaths and complications (e.g. volvulus, gastrointestinal bleeding, strangulation) of patients with giant paraesophageal hernia that were conservatively managed, and to determine factors associated with clinical outcome.

Methods

We retrospectively analyzed charts of patients diagnosed with giant paraesophageal hernia between January 1990 and August 2019, collected from a university hospital in The Netherlands. Included patients were subdivided into three groups based on primary therapeutic decision at diagnosis. Radiological, clinical and surgical characteristics, along with long-term outcomes at most recent follow-up, were collected.

Results

We included 293 patients (91 men, mean age 70.3 ± 12.4 years) with a mean duration of follow-up of 64.0 ± 58.8 months. Of the 186 patients that were conservatively treated, a total hernia-related mortality of 1.6% was observed. Hernia-related complications, varying from uncomplicated volvulus to strangulation, occurred in 8.1% of patients. Only 1.1% of patients included in this study required emergency surgery. Logistic regression analysis revealed the presence of symptoms (odds ratio (OR) 4.4, 95% confidence interval (CI) 1.8–20.6), in particular obstructive symptoms (vomiting, OR 15.7, 95% CI 4.6–53.6; epigastric pain, OR 4.4, 95% CI 1.2–15.8 and chest pain, OR 6.1, 95% CI 1.8–20.6) to be associated with the occurrence of hernia-related complications.

Conclusions

Hernia-related death and morbidity is low in conservatively managed patients. The presence of obstructive symptoms was found to be associated with the occurrence of complications during follow-up. Conservative therapy is an appropriate therapeutic strategy for asymptomatic patients.

INTRODUCTION

Diaphragmatic herniation is a common condition involving the gastrointestinal tract. It is characterized by a protrusion of the stomach and/or other intraabdominal content into the chest cavity through a widening between both slings of the right crus of the diaphragm.[1] Hiatal hernia can be categorized in four anatomical patterns.[2] By far the most common type of hiatal hernia and strongly associated with gastroesophageal reflux is a sliding or type I hiatal hernia in which the gastroesophageal junction migrates above the diaphragm.[1] Type II or a paraesophageal hernia represents only 5% of all hiatal hernias, with herniation of the gastric fundus adjacent to a normally positioned esophagogastric junction. Type III hernia is a combination of both types I and II. Often, due to a progressive enlargement of hiatus and herniation, these hernias tend to be of considerable size, taking up a great part of the thoracic cavity.[3] Type IV represents a more complex type of hernia, with complete migration of other intraabdominal viscera such as small bowel or colon in the hernia sac. Definitions of the terms 'intrathoracic stomach' or 'giant' paraesophageal hernia appear inconsistently in the literature, but most authors limit these terms to those paraesophageal hernias having greater than one-third of the stomach in the thorax.[1,3–6]

A giant paraesophageal hernia can present itself in a wide variety of forms, ranging from an incidentally detected hernia without symptoms, to a gastric volvulus with risk of ischemia. Dysphagia, reflux or obstructive symptoms such as postprandial pain and vomiting are reported.[1] In addition, respiratory symptoms as a result of pulmonary compression, or gastrointestinal bleeding due to reflux esophagitis and ulceration may occur. A gastric volvulus is a very rare but major complication associated with paraesophageal hernia, and may lead to gastric bleeding, incarceration and strangulation causing bowel obstruction, ischemia and/or perforation.[7,8] The need for surgical correction in asymptomatic, or mildly symptomatic patients is an ongoing matter of debate. Despite the fact that the finding of giant paraesophageal hernia is incidental in a large subset of patients, it is believed that potentially life-threatening complications may occur if the hernia is not surgically managed.[9] However, the majority of this patient population is often of advanced age with extensive comorbidity, making them poor surgical candidates.

Traditionally, elective surgery was often advocated for every patient, in spite of symptoms, with the objective of preventing acute complications and to avoid significant mortality and morbidity associated with emergency surgery.[7,8,10–14] While more recent series suggest that the occurrence of life-threatening complications in untreated patients as well as the mortality rates for emergency surgery are much lower than initially estimated.[15–18] However, all current knowledge on the true natural course of a giant paraesophageal hernia derives from older, small series with a limited duration of follow-up. Due to the paucity of long-term observational cohort studies, information on the natural course and complication risk of untreated giant paraesophageal hernia is scarce and the indication for elective hernia repair in mildly

symptomatic patients remains a subject of discussion. In the present study we were able to identify a substantial cohort of conservatively treated patients with giant paraesophageal hernia over almost three decades. Our aim was to describe the long-term outcomes of these patients and to determine characteristics associated with clinical outcome.

METHODS

Study design

We retrospectively studied a cohort of patients diagnosed and followed up at the gastroenterology and surgery departments of the Amsterdam University Medical Center. Patients diagnosed with a giant paraesophageal hernia were identified through radiology reports. Electronic charts were critically assessed and relevant data were extracted. Missing chart documentation at follow-up was obtained by means of telephone interviews.

Patient selection

All radiography, computed tomography (CT) and barium esophagogram reports between January 1990 and August 2019 were searched with a query based on the keywords 'intrathoracic stomach' and 'paraesophageal hernia'. The full search query is detailed in **Supplemental Table 1**. Electronic charts of the retrieved patient numbers were independently screened for eligibility by two reviewers (RON and MH). In case of uncertainty, charts were re-reviewed by a third reviewer (AJB) until consensus was reached. We included adult patients with the radiological diagnosis of a giant paraesophageal hernia, defined as herniation of at least one-third of the stomach into the thoracic cavity.[1,3–6] Exclusion criteria were: the presence of congenital or traumatic hernia or a history of esophageal surgery or radiation therapy. Relevant data from eligible patients were extracted and registered in an electronic patient record system (Castor EDC, The Netherlands). Extracted information included demographics (e.g. age, sex, body mass index (BMI)), clinical characteristics (age at symptom onset, age at diagnosis, medical history, medication use and intoxications), and disease-specific characteristics (symptoms, radiological and endoscopic findings).

Clinical and radiological characteristics

Symptoms were extracted from patient charts and scored as either present or absent, based on the clinical assessment and recording of the treating physician at the time of diagnosis and at latest follow-up. Extracted symptoms included: epigastric pain, heartburn, dysphagia, chest pain, weight loss, bloating, dyspepsia, postprandial fullness, regurgitation, dyspnea, hematemesis and belching. Both age at diagnosis and age at onset of symptoms were retrieved. Endoscopic data were extracted from endoscopy reports. Reports were screened for signs of reflux esophagitis, Barrett's esophagus, the presence of Cameron lesions, malignancies and ulcer disease. Radiology reports were screened for hernia size, hernia type (sliding, paraesophageal or combined) and the involvement of other abdominal

organs as reported by the radiologist.

Treatment characteristics

Included patients were subdivided into three groups based on the primary therapy they received; elective surgery, emergency surgery or conservative therapy. Conservative treatment was defined as any type of medical treatment other than surgery. In the case of primary surgical treatment, the procedure time, surgical approach (abdominal or thoracic), type (laparotomy or laparoscopic), addition of anti-reflux procedure, and the American Society of Anesthesiologists (ASA) physical status classification were extracted. The decision to operate in the elective setting was made by the treating physician for each patient individually and based on the type and extent of symptoms, a patient's quality of life and surgical risk.

Long-term outcomes

As the main objective of this study was to explore the natural history of giant paraesophageal hernia, we extracted follow-up data for the conservatively managed patients. Data on the presence and type of symptoms, current medication use, occurrence of any hernia-related events or complications during the course of follow-up were collected at the time of latest available follow-up visit. All hernia-related events that required acute intervention or hospital admission were reported as a complication and were divided into: obstructive complications with or without ischemia, esophageal or gastric perforation, cardiac or respiratory failure and acute bleeding. Finally, the vital status and cause of death were extracted. In deceased patients, in whom the cause of death could not be obtained, general practitioners were contacted for information. In the case of missing follow-up documentation, patients were contacted and questionnaires by telephone were conducted to assess current health status, the presence of symptoms, the occurrence of any (acute) hernia-related events, or hospital admissions. An uneventful follow-up was defined as the absence of complications, elective surgical hernia repair, symptom progression or hernia-related death at the end of follow-up.

Ethics

The study protocol was reviewed by the local institutional review board (IRB) and as this was a retrospective study and patients were not exposed to any additional interventions for the study purpose, it was confirmed that the Medical Research Involving Human Subjects Act did not apply (reference number W19_228#19.274).

Statistical analysis

SPSS statistics (version 24; SPSS, Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were presented as a percentage for categorical data and as means with standard deviations for continuous variables. Due to retrospective non-standardized data collection, not all included patients had a complete dataset, therefore all results

are presented as percentages of the total number of patients for whom the concerning variable was available. Mann–Whitney U or χ^2 tests were used to compare variables when appropriate. Annualized risk rates were expressed as percentages and calculated by the number of hernia-related events divided by the number of patient-years follow-up. Of note, these annual rates were calculated under the assumption that annual risk is constant over time and independent of disease duration. To explore factors associated with the occurrence of hernia-related complications univariate logistic regression analysis was performed.

RESULTS

Patient selection

We retrieved a cohort of 466 patients with a potential radiological diagnosis of giant paraesophageal hernia. After an initial screening and the removal of duplicates, 342 patients with a confirmed diagnosis of giant paraesophageal hernia were identified. Patients younger than 18 years at the time of diagnosis (*n* = 23) and patients who did not give consent for data extraction (*n* = 7) were excluded. After critical appraisal of these 342 patient files, another 49 patients were excluded because of congenital (*n* = 6) or traumatic hernia (*n* = 3), less than one-third of the stomach in the chest cavity (*n* = 17), a history of esophageal surgery (*n* = 6), or esophageal radiation therapy (*n* = 3). Seven patients were excluded due to incomplete or missing chart documentation. Ultimately, 293 patients met the diagnostic definition of a giant paraesophageal hernia and fulfilled our inclusion and exclusion criteria. Subject identification and recruitment is presented in **Figure 1**.

Patient characteristics

Of the 293 included patients 91 (31.1%) were men. Patients' mean age at diagnosis was 70.3 ± 12.4 years. Of the 289 patients for whom the medical history was known, a subset had chronic comorbidities, including ischaemic heart disease (*n* = 40, 13.8%), arterial vascular disease (*n* = 34, 11.8%), chronic obstructive pulmonary disease (*n* = 32, 11.1%) or a history of diabetes mellitus (*n* = 30, 10.4%). A complete overview of patients' characteristics and medical history is presented in **Table 1**.

Symptoms and endoscopic findings

The majority of patients (*n* = 179, 61.1%) presented with symptoms at diagnosis. Heartburn (*n* = 61, 21.5%), respiratory symptoms (*n* = 61, 21.5%), epigastric pain (*n* = 51, 18.0%) and dysphagia (*n* = 42, 14.8%) were the most frequently reported symptoms (**Table 2**). Other less commonly exhibited symptoms were nausea or vomiting (*n* = 39, 13.7%), chest pain (*n* = 38, 13.4%), weight loss (*n* = 24, 8.5%), regurgitation (*n* = 22, 7.7%), postprandial fullness (*n* = 15, 5.3%), and belching (*n* = 6, 2.1%). Twenty-five (8.5%) patients presented with one or multiple hernia-related complications at the time of diagnosis. Obstruction and gastrointestinal bleeding were predominantly reported (60.0% and 24.0%, respectively). A

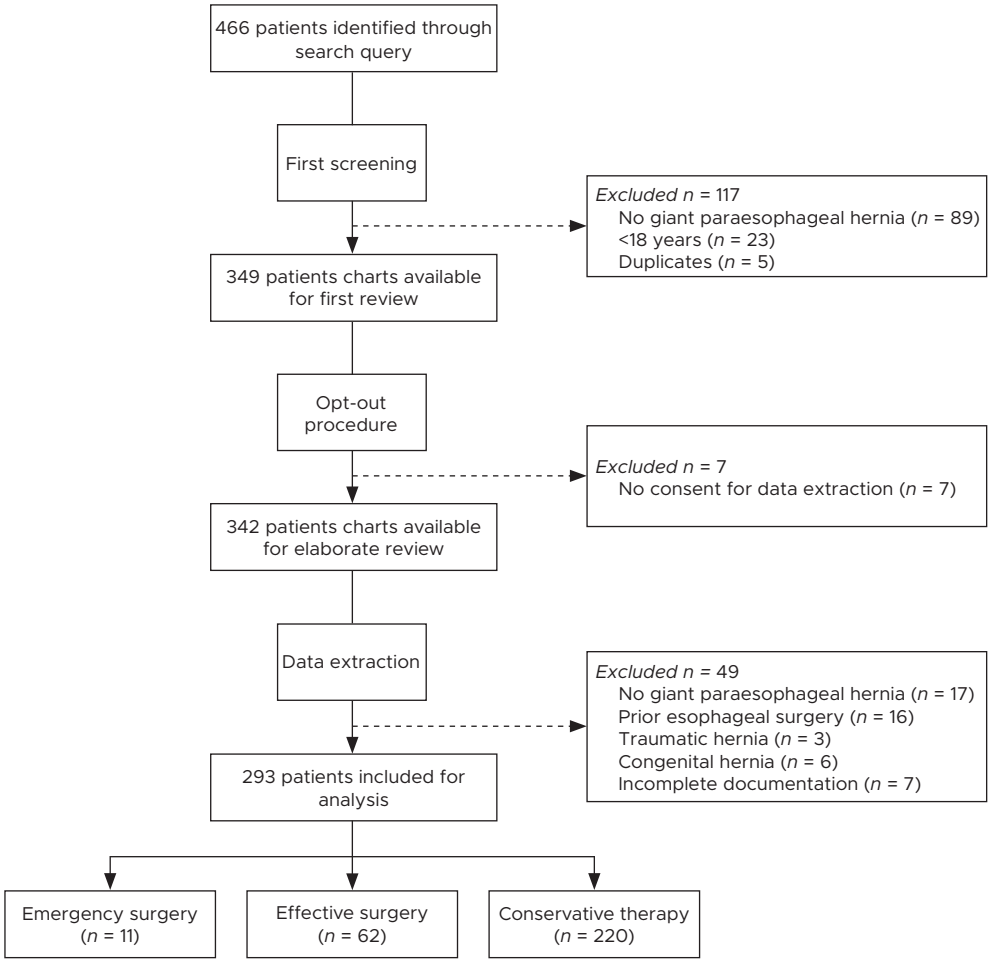

Figure 1. Flowchart of case findings

subset of patients (38.9%) presented asymptomatically. In 166 (59.2%) patients the finding of a giant paraesophageal hernia was discovered incidentally. Iron deficiency anemia was found in 50 of the 274 patients (18.2%) in whom laboratory results were reported. Upper endoscopy was performed in 111 patients. We identified 16 patients (14.4%) with reflux esophagitis, 13 patients (11.7%) with concomitant Barrett's esophagus, seven patients (6.3%) with Cameron lesions and four patients (3.7%) with gastric ulcers at endoscopic inspection.

Radiological characteristics

Diagnosis was established with CT in 52 (17.7%) patients (**Table 3**). Fifty-six (19.1%) patients and 91 (32.1%) patients were diagnosed by means of barium esophagram and chest radiography, respectively. In the majority of patients (*n* = 94, 32.1%) a combination of

diagnostic tests (e.g. CT, esophagram and radiography) were performed to establish the diagnosis of giant paraesophageal hernia. Type III hiatal hernia was most often reported (90.8%). Type IV was described in only 27 (9.2%) patients.

Primary therapy

All included patients were categorized based on the primary therapeutic decision at the time of diagnosis. The characteristics of patients who received conservative treatment (*n* = 220) and elective surgery (*n* = 62) are displayed separately in **Tables 1, 2 and 3**. The characteristics of patients who underwent emergency surgery at baseline (*n* = 11) are displayed in **Supplemental Table 2**. In patients who were conservatively treated, the majority of patients (*n* = 129, 58.6%) used or were started on pharmacological therapy. Proton pump inhibitors were most frequently used (54.5%), followed by H_2-receptor antagonists (6.4%) and prokinetic drugs (5.0%). Twenty-five (8.5%) patients presented with hernia-related complications at the time of diagnosis, of whom 11 (3.8%) (median age 72 years, interquartile range (IQR) 46–74) underwent emergency surgery. These complications are specified in **Supplemental Table 3**. One patient underwent a laparotomic partial gastric resection. In the remaining 10 patients an emergency hernia correction was performed, of whom eight underwent an open procedure. In the elective surgery group, specific information on the type of surgical procedure was available in 58 patients. The majority of patients (70.6%) underwent laparoscopic hernia repair. An anti-reflux procedure was performed in 42 out of 58 patients (72.4%), this was a Toupet fundoplication in half of the cases. Cruroplasty was performed in all 58 patients, while mesh-based reinforcement was used in only 8.6% of patients. The surgical characteristics of patients treated electively or emergently are displayed in **Supplemental Table 4**.

Differences in surgically and conservatively treated patients

Conservatively treated patients were younger (P < 0.001) and had higher ASA scores (3) (P < 0.001) (**Table 1**). With regard to symptoms, patients who underwent elective surgery were symptomatic in all cases, whereas 48.2% of patients in the conservative treatment group presented with symptoms (P < 0.001) (**Table 2**). The majority of symptoms; for example, dysphagia, heartburn, epigastric pain, regurgitation, postprandial fullness, chest pain and nausea were predominantly observed in patients who were treated with an elective operation.

Clinical course and long-term follow-up in the elective surgery group

In the elective surgery group, intraoperative or postoperative complications occurred in 12 (22.2%) and nine (16.7%) patients, respectively (**Supplemental Table 5**). Follow-up data could be obtained for 60 of the 62 patients who underwent elective surgery. The median follow-up time in this group was 33 (IQR 12–106) months. After surgery, 33 (53.3%) patients became symptomatic, this included any recurrent or new postoperative complaints during

Table 1. Baseline characteristics in patients with giant paraesophageal hernia

	Total study population (n = 293)			Conservative (n = 220)	Surgical (n = 62)	
Clinical characteristics	**n^a/N^b**	**%**	**Mean (SD) or median (IQR)**	**n^a/N^b (%)**	**n^a/N^b (%)**	**P value**
Sex						0.867
Male	91/293	31.1		65/220 (29.5)	19/62 (30.6)	
Female	202/293	68.9		155/220 (70.5)	43/62 (69.4)	
Age at diagnosis (years), mean (SD)			70.3 (12.4)	73.0 (11.6)	61.8 (9.6)	**<0.001**
Caucasian	220/293	75.1		165/220 (75.0)	47/62 (75.8)	0.897
BMI,[c] median (IQR)			27.02 (4.7–31.1)	28.9 (24.7–31.1)	27.7 (25.0–31.6)	0.360
ASA ≥3	86/288	29.9		79/215 (36.7)	2/62 (3.2)	**<0.001**
Intoxications						
History of smoking	76/211	36.0		56/164 (34.1)	18/62 (40.0)	0.467
Alcohol use >2 units per day	21/196	10.7		18/152 (11.8)	3/43 (7.0)	0.364
Medical history						
Cardiac disease	40/289	13.8		34/216 (15.7)	4/62 (6.5)	0.061
Vascular disease	34/289	11.8		27/216 (12.5)	5/62 (8.1)	0.335
COPD	32/289	11.1		24/216 (11.1)	8/62 (12.9)	0.697
Diabetes mellitus	30/289	10.4		23/216 (10.6)	7/62 (11.3)	0.886
Concomitant esophageal carcinoma	9/293	3.1		8/220 (3.6)	1/62 (1.6)	0.423

ASA: American Society of Anesthesiologists; BMI: body mass index; IQR: interquartile range; COPD: chronic obstructive pulmonary disease; SD: standard deviation.

[a]Number of patients.

[b]Total number of patients in whom data could be obtained.

[c]n = 173.

Bold values denote statistical significance at the P < 0.05 level.

Table 2. Clinical, endoscopic and radiological characteristics of patients with giant paraesophageal hernia

	Total study population (*n* = 293)		Conservative (*n* = 220)	Surgical (*n* = 62)	
Characteristics	***n*[a]/*N*[b]**	**%**	***n*[a]/*N*[b] (%)**	***n*[a]/*N*[b] (%)**	**P value**
Symptoms at diagnosis	179/293	61.1			
Asymptomatic	114/293	38.9	114/220 (51.8)	0/62(0.0)	**<0.001**
Incidental finding	166/280	59.3	159/215(74.0)	4/55(7.3)	**<0.001**
Type of symptoms					
Heartburn	61/284	21.5	36/213 (16.9)	25/61 (41.0)	**<0.001**
Respiratory symptoms	61/284	21.5	41/213 (19.2)	18/61 (29.5)	0.086
Epigastric pain	51/284	18.0	21/213 (9.9)	26/61 (42.6)	**<0.001**
Dysphagia	42/284	14.8	17/213 (8.0)	24/61 (39.3)	**<0.001**
Nausea and/or vomiting	39/284	13.7	21/213 (9.9)	13/61 (21.3)	**0.017**
Chest pain	38/284	13.4	20/213 (9.4)	16/61 (26.2)	**0.001**
Weight loss	24/284	8.5	9/213 (4.2)	14/61 (23.0)	**<0.001**
Regurgitation	22/284	7.7	7/213 (3.3)	15/61 (24.6)	**<0.001**
Postprandial fullness	15/284	5.3	8/213 (3.8)	7/61 (11.5)	**0.019**
Belching	6/284	2.1	3/213 (1.4)	3/61 (4.9)	0.099
Hernia-related complications	25[c]/293	8.5	11/220 (5.0)	3/62 (4.8)	0.959
Obstruction	15	60.0			
Gastrointestinal bleeding	6	24.0			
Obstruction with ischemia	4	16.0			
Respiratory/cardiac compression	2	8.0			
Gastric/esophageal perforation	1	4.0			
Laboratory findings					
Iron deficiency anemia	50/274	18.2	42/208 (20.2)	7/57 (12.3)	0.173
Endoscopic findings					
Reflux esophagitis	16/111	14.4	7/68 (10.3)	8/40 (20.0)	0.159
Cameron lesions	7/111	6.3	3/68 (4.4)	4/40 (10.0)	0.255
Barrett's esophagus	13/111	11.7	7/68 (10.3)	5/40 (12.5)	0.725
Gastrointestinal ulcer(s)	4/111	3.6	4/68 (5.9)	0/40 (0.0)	0.118

[a]Number of patients.
[b]Total number of patients in whom data were obtained.
[c]Number of patients with one or multiple hernia-related complications at diagnosis.
Bold values denote statistical significance at the P < 0.05 level.

Table 3. Radiological diagnosis of patients with giant paraesophageal hernia

	Total study population (*n* = 293)	Conservative (*n* = 220)	Surgical (*n* = 62)	P value
	n[a]/*N*[b]	*n*[a]/*N*[b] (%)	*n*[a]/*N*[b] (%)	
Radiological diagnosis				
CT scan	52/293 (17.7)			
Chest radiograph	91/293 (31.1)			
Barium esophagram	56/293 (19.1)			
Combination of tests listed above	94/293 (32.1)			
Hernia anatomy				0.976
Type III hiatal hernia	266/293 (90.8)	202/220 (91.8)	57/62 (91.9)	
Type IV hiatal hernia	27/293 (9.2)	18/220 (8.2)	5/62 (8.1)	

CT: computed tomography.
[a]Number of patients.
[b]Total number of patients in whom data were obtained.

the postoperative course. Of these patients, hernia recurrence was confirmed by radiology in 19 (31.7%) patients, of whom 11 patients underwent redo surgery. Two patients presented with acute symptoms and underwent emergency surgery; both patients presented with gastric perforation due to gastric obstruction with ischemia. There were no (hernia-related) deaths in the elective surgery group.

Long-term follow-up in conservatively treated patients

Follow-up data could be obtained in 186 conservatively treated patients and are summarized in **Figure 2**. The mean duration of follow-up of this group was 58 (IQR 31–106) months. The majority of patients (64.0%) reported no changes in clinical course or any hernia-related events. Sixty-seven (36.0%) patients experienced a hernia-related event in the course of follow-up, of whom 39 (58.2%) patients reported symptom progression that could still be managed conservatively. In 13 (7.0%) patients symptoms worsened in such a way that elective hernia repair was indicated. Hernia-related complications occurred in 15 (8.1%) patients, of which three (1.6%) were classified as gangrenous complications (**Supplemental Table 6**). Two (1.1%) patients underwent emergency surgery because of strangulation and gastric perforation. The corresponding annual risks for requiring emergency surgery and developing a hernia-related complication were 0.2% per annum and 1.7% per annum, respectively. One of the patients died shortly after surgery due to septic shock. Two patients did not undergo emergency surgery because of extensive comorbidity and died from their complications; one patient from obstruction with respiratory failure and the other due to severe gastric bleeding. The remaining 11 patients could be managed either semi-

electively (*n* = 4) or conservatively (*n* = 7). Of all 220 conservatively treated patients, 96 (43.6%) patients had died during the course of follow-up. We were able to obtain the cause of death in the majority (83.3%, *n* = 80) of these patients. As mentioned earlier, three (1.6%) patients of the 186 patients in whom follow-up data could be obtained, eventually died from a hernia-related complication.

Risk factors for hernia-related complications in conservatively treated patients

To determine risk factors for hernia-related complications in patients who were conservatively managed, we performed a logistic regression analysis with the occurrence of complications as a dependent variable (**Table 4**). Univariate analysis identified the presence of symptoms at diagnosis (OR 4.44; 95% CI 1.21–16.31; P = 0.025), epigastric pain (OR 4.37; 95% CI 1.21–15.76; P = 0.024), chest pain (OR 6.07; 95% CI 1.79–20.62; P = 0.004), vomiting (OR 15.70; 95% CI 4.60–53.56; P < 0.001) and Cameron lesions (OR 17.00; 95% CI 1.33–216.67; P = 0.029) as risk factors for the occurrence of hernia-related complications.

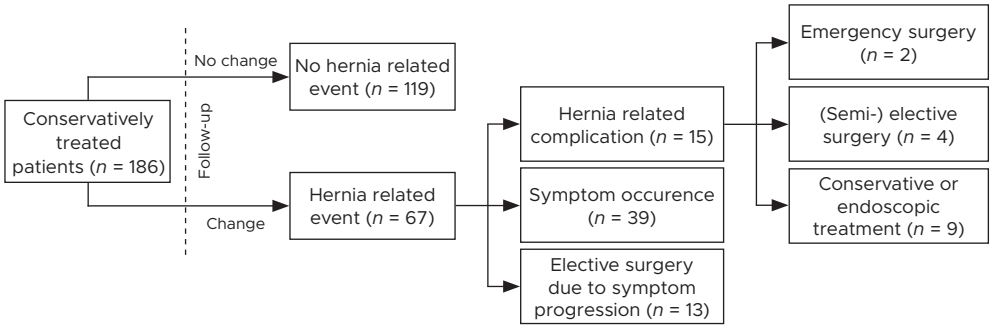

Figure 2. Long-term outcomes in the 186 conservatively treated patients in whom follow-up data could be obtained

Table 4. Logistic regression analysis for identifying risk factors for 'hernia-related complications' in conservatively treated patients

	Univariable		
Demographic and clinical characteristic	**OR**	**95% CI**	**P value**
Male sex	2.117	0.729–6.125	0.168
Age	1.019	0.969–1.071	0.462
BMI	0.991	0.912–1.076	0.830
ASA 2:3	0.273	0.059–1.261	0.096
Smoking	1.533	0.502–4.658	0.453
Alcohol use >2 units/day	2.850	0.688–11.799	0.149
Use of risk medication[a]	0.331	0.041–2.643	0.297
Disease-specific characteristics			
Hernia type IV	2.477	00.490–12.515	0.272
Complete herniation of stomach in chest cavity	2.183	0.733–6.507	0.161
Presence of symptoms at diagnosis	4.444	1.211–16.312	**0.025**
Duration of symptoms	2.183	0.733–6.507	0.161
Type of symptoms at diagnosis			
Dysphagia	2.153	0.431–10.749	0.350
Postprandial fullness	4.472	0.813–24.588	0.085
Heartburn	1.151	0.303–4.366	0.837
Respiratory symptoms	1.107	0.292–4.197	0.085
Regurgitation	–	–	–
Chest pain	6.071	1.788–20.617	**0.004**
Epigastric pain	4.371	1.213–15.757	**0.024**
Belching	12.769	0.755–216.100	0.078
Weight loss	1.758	0.201–15.402	0.610
Nausea/vomiting	15.700	4.602–53.566	**<0.001**
Iron deficiency anemia	0.593	0.127–2.770	0.506
Endoscopic findings			
Reflux esophagitis	1.714	0.167–17.626	0.650
Cameron lesions	17.000	1.334–216.666	**0.029**
Barrett	–	–	–
Ulcer(s)	3.571	0.285–44.718	0.324

ASA: American Society of Anesthesiologists; BMI: body mass index; CI: confidence interval; OR: odds ratio.
[a]Risk medication was defined as medication associated with a potentially damaging effect on gastric mucosa, such as anticoagulants, corticosteroids, selective serotonin re-uptake inhibitors or non-steroidal anti-inflammatory drugs.
Bold values denote statistical significance at the $P < 0.05$ level.

DISCUSSION

The management and indication for surgical repair of giant paraesophageal hernias remained a topic of discussion for decades. Despite ongoing controversies, accurate information on the natural course of paraesophageal hernia is scarce. In the present study we were able to identify a large cohort of patients over almost three decades. A comprehensive analysis of 293 patients was conducted and, radiological, clinical, endoscopic and surgical features were identified and stratified by primary therapeutic decision. The results of this study strongly support the view that elective repair of a giant paraesophageal hernias is not required in all patients. We demonstrated that hernia-related death in conservatively treated patients, followed up for a median of 58 months, is rare; in 186 patients, a total hernia-related mortality of 1.6% was observed. Although hernia complications, varying from uncomplicated volvulus to strangulation, occurred in 8.1% of our patients, only 1.1% of these patients required emergency surgery. The majority could be managed either endoscopically or conservatively. We demonstrated that symptomatic patients have a 4.4-fold higher risk of developing a hernia-related complication. In particular, obstructive symptoms, including epigastric pain and vomiting, were found to be associated with the occurrence of complications at a later time. In addition, as a result of the generally high age in this patient group, almost all of the deceased patients in our cohort eventually died from other comorbid diseases.

The dictum that all paraesophageal hernias should be repaired electively irrespective of symptoms, derived from early reports that raised concerns of high complication rates, suffered from patients left untreated.[7,8,19] The occurrence of potentially life-threatening complications were described in up to 29% of the patients.[7,8] However, in the years that followed, several surgeons and investigators have been questioning the benefit of performing elective hernia repair in mildly symptomatic or asymptomatic patients. Allen and colleagues described 23 unoperated patients, who were followed for a mean of 6.5 years. None developed hernia-related complications or required emergency surgery.[15] Treacy and Jamieson evaluated 29 untreated patients, and in spite of the 13 (45%) patients who required elective surgery for progression of symptoms, none had to be treated emergently.[16] More than a decade later, the surgical viewpoint was further undermined by a report using population-based decision analysis modeling to conclude that the mortality rate of elective hernia repair was 1.4%, whereas the annual probability of developing a hernia-related complication was only 1.1%.[17] A more recent study showed that gangrenous complications occurred in only 0.9% of patients admitted from 1998 to 2008 for giant paraesophageal hernia.[20] This is in line with our findings; of the unoperated patients, only 1.6% developed volvulus with strangulation or ischemia. Of note, we found a higher total complication rate of 8% for untreated paraesophageal hernia than Stylopoulus and colleagues, as they specified complications only as obstructed or strangulated hernia, whereas we also included bleeding from reflux esophagitis or gastrointestinal ulcers.[17] Nevertheless, our estimated rate of 1.1%

for requiring emergency surgery is in accordance with the results from the aforementioned study. In this respect, our findings are in keeping with the more recent reports that suggest that symptom progression is slow and is less likely to evolve to acute symptoms than previously expected.

As mentioned earlier, the rationale behind the shifting surgical dictum is twofold; besides the low complication rates in unoperated patients, the more recent studies also demonstrated that mortality for emergency surgery was much lower than initially believed. Previously, early studies advocated elective surgery in all patients because of reported mortality rates up to 17% for emergency surgery,[8] whereas the more recent studies have shown that the mortality of emergency surgical repair was presumably overestimated in early reports, and is more likely to be between 0.4% and 5%.[17,21] In line with this, we found rather high complication rates in our elective surgery group, most likely explained by the fact that we included a subset of patients who underwent surgery in the early 1990s, while more recent series show that outcomes after elective surgery have improved tremendously with new advancements in laparoscopic or robot-assisted hernia repair.[22] Our study shows that the overall risk of the occurrence of acute complications of giant paraesophageal hernia in conservatively managed patients in time is low. Therefore, we support the standpoint that conservative management is an appropriate strategy for asymptomatic or moderately symptomatic patients with giant paraesophageal hernia. This applies in particular for elderly or frail patients, in whom this condition is most commonly found and who often have extensive comorbidities. A large subset of our conservatively managed patients died of other comorbid diseases before the end of follow-up. Hence, besides the fact that these patients are often poor surgical candidates to begin with, another argument for deferring elective surgery in this group is that the vast majority will most likely die from other comorbid diseases.

Many considerations must be taken into account when formulating therapeutic strategies for patients with giant paraesophageal hernia, and it is with good reason that hernia repair of this subgroup remains one of the most widely debated and controversial areas in surgery. What recommendations can be made in terms of therapeutic decision-making? First, standard elective operation is not necessarily required in all mild to moderately symptomatic patients. Especially in older patients, who are in general considered to be less fit for surgery, watchful waiting is a valuable therapeutic alternative. Pharmacological or endoscopic therapy may be sufficient for symptom control in a subset of patients. Second, symptomatic patients should be consulted by a foregut surgeon to discuss definitive surgical repair. The decision to operate in the elective setting should largely depend on the type and extent of a patient's symptoms. Symptoms secondary to mechanical obstruction are more concerning for subsequent volvulus, whereas non-obstructive symptoms including gastroesophageal reflux can often be managed pharmacologically. We emphasize the

importance of a thorough clinical evaluation and counseling by an upper gastrointestinal surgeon, in which the risk–benefit profile of definitive repair versus observation is weighed, taking into account the extent and type of symptoms, hernia anatomy, a patient's age and perioperative risk.

This study has some limitations. First, the findings of this study should be appraised while keeping in mind that patients were selected from one academic healthcare center, which could have led to selection bias. Second, the results are based on retrospective analysis of patients' charts in which data were not uniformly registered. Therefore, we were unable to obtain complete and standardized datasets of all patients. In addition, we had to rely on the clinical evaluation, registration and decision of the treating physicians, which may have induced bias as well. In line with this, the number of symptomatic patients may be underestimated. Expert opinion suggests that truly asymptomatic paraesophageal hiatal hernias do exist, but are rare. Nevertheless, to minimize these limitations, stringent inclusion and exclusion criteria were used, charts were critically appraised by two or three reviewers, and missing chart documentation at followup was obtained through telephone interviews.

In conclusion, this is the largest available study reporting on the natural course of giant paraesophageal hernia. We showed that hernia-related death and morbidity is low in conservatively treated patients. Therefore, conservative management is an appropriate therapeutic strategy for asymptomatic patients.

AUTHOR CONTRIBUTIONS

RON, AJB, MS, WAD and AJPMS played a role in planning of the study. RON, MH and AJB had a role in conducting the study. RON and MH were involved in the acquisition of data. RON, MH, JMS and AJB had a role in collecting and/or interpreting data. RON and MH played a role in drafting the manuscript. MS, WAD, AJPMS, JMS and AJB played a role in reviewing and revising the manuscript for important intellectual content. All authors approved the final draft submitted.

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Query used to search all radiology reports from January 1990 until August 2019 with the keywords 'intrathoracic stomach' and 'paraesophageal hernia'

1)	'Intrathoracale maag' 'intrathoracaal gelegen maag' Simplified to: %Intrathoraca%maag%
2)	'(grote*) paraoesofageale (hiatus*)hernia' 'para-oesofageale hernia' 'paraoesophageale hernia' 'para-oesophageale hernia' Simplified to: %para%oeso%ageale%hernia%

Supplemental Table 2. Baseline characteristics of patients who underwent emergency surgery

Demography	n[a]/N[b]	%	Mean(SD)
Sex			
Male	7/11	63.6	
Female	4/11	36.4	
Age at diagnosis (years), mean (SD)			65.5 (18.9)
Caucasian	8/11	72.7	
BMI[c], median (IQR)			23.1 (3.3)
ASA ≥3	5/11	45.5	
Medical history			
Cardiac disease	2/11	18.1	
Vascular disease	2/11	18.1	
COPD	0/11	0.0	
Diabetes mellitus	0/11	0.0	
Concomitant esophageal carcinoma	0/11	0.0	
Symptoms at diagnosis	11/11	100.0	
Heartburn	0/11	0.0	
Respiratory symptoms	2/11	18.1	
Epigastric pain	4/11	36.4	
Dysphagia	1/11	9.1	
Nausea and/or vomiting	5/11	45.5	
Chest pain	2/11	18.1	
Weight loss	1/11	9.1	
Regurgitation	0/11	0.0	
Postprandial fullness	0/11	0.0	
Belching	0/11	0.0	
Iron deficiency anemia	1/9	11.1	
Endoscopic findings			
Reflux esophagitis	1/3	33.3	
Cameron lesions	0/3	0.0	
Barrett's esophagus	1/3	33.3	
Gastrointestinal ulcer(s)	0/3	0.0	
Radiologic diagnosis			
CT scan	5/11	45.5	
Chest radiograph	5/11	45.5	
Barium esophagram	1/11	9.1	
Hernia anatomy			
Type III hiatal hernia	7/11	63.6	
Type IV hiatal hernia	4/11	36.4	

[a]Number of patients.
[b]Total number of patients in whom data could be obtained.
[c]*n* = 2
ASA, American Society of Anesthesiologists classification; BMI, body mass index; COPD, Chronic Obstructive Pulmonary Disease; IQR, Inter Quartile Range; SD, Standard Deviation.

Supplemental Table 3. Patients with an acute complication that underwent emergency surgery at baseline

Patient	Age (years)	Sex	Type of complication (*n* = 11)
1	70	M	Obstruction
2	74	M	Obstruction with ischemia
3	74	F	Obstruction
4	70	M	Obstruction
5	28	M	Obstruction
6	85	M	Cardiac compression
7	88	F	Obstruction
8	46	F	Obstruction with ischemia
9	72	M	Gastrointestinal bleeding
10	40	M	Obstruction with ischemia and gastrointestinal bleeding
11	73	F	Obstruction with ischemia and perforation

Supplemental Table 4. Surgical characteristics in patients who underwent elective and emergency surgery at baseline

	Elective surgery (*n* = 60)		Emergency surgery (*n* = 11)	
	n[a]/*N*[b]	(%)	*n*[a]/*N*[b]	(%)
Type of repair				
Laparoscopic hernia repair	41/58	70.6	2/11	18.2
Open hernia repair	17/58	29.3	8/11	72.7
Open gastric resection	-	-	1/11	9.1
Hiatal closure				
Suture-based	58/58	100.0	11/11	100.0
Mesh-reinforced	5/58	8.6	0/11	0.0
Anti-reflux procedure	42/58	72.4	3/11	27.3
Toupet	21	50.0	1	33.3
Nissen	15	35.7	2	66.7
Dor	1	2.4	0	0.0
Unknown	5	11.9	0	0.0
Surgical details				
Transabdominal approach	58/58	100.0	11/11	100.0
Gastropexy	36/49	73.5	6/11	54.5
Hernia sac excision	36/54	66.7	8/11	72.7
Operation time in minutes, mean (SD)	135.3	55.1	128.1	32.0

[a]Number of patients.
[b]Total number of patients of whom data was obtained.
SD, standard deviation.

Supplemental Table 5. Perioperative outcomes in patients who underwent elective and emergency surgery at baseline

	Elective surgery (*n* = 60)		Emergency surgery (*n* = 11)	
	n[a]/N[b]	(%)	n[a]/N[b]	(%)
Intraoperative complications	12/54	22.2	2/11	18.2
Splenic laceration	4		1	
Esophageal or gastric perforation	2		0	
Opening pleura	3		1	
Vagal nerve ligation	2		0	
Subcutaneous emphysema	1		0	
Postoperative complications	9/54	16.7	2/11	18.2
Cardiac arrhythmia	2		-	
Wound infection	1		-	
Bleeding	1		-	
Incisional hernia	4		-	
Pneumonia	1		1	
Infection of haematoma	-		1	
Length of hospital stay in days, median(IQR)*	5.0[c]	(3.0-100)	9.0	(7.5-19)
In-hospital mortality	0/62	0	2/11	18.2
Sepsis/SIRS	-		2	

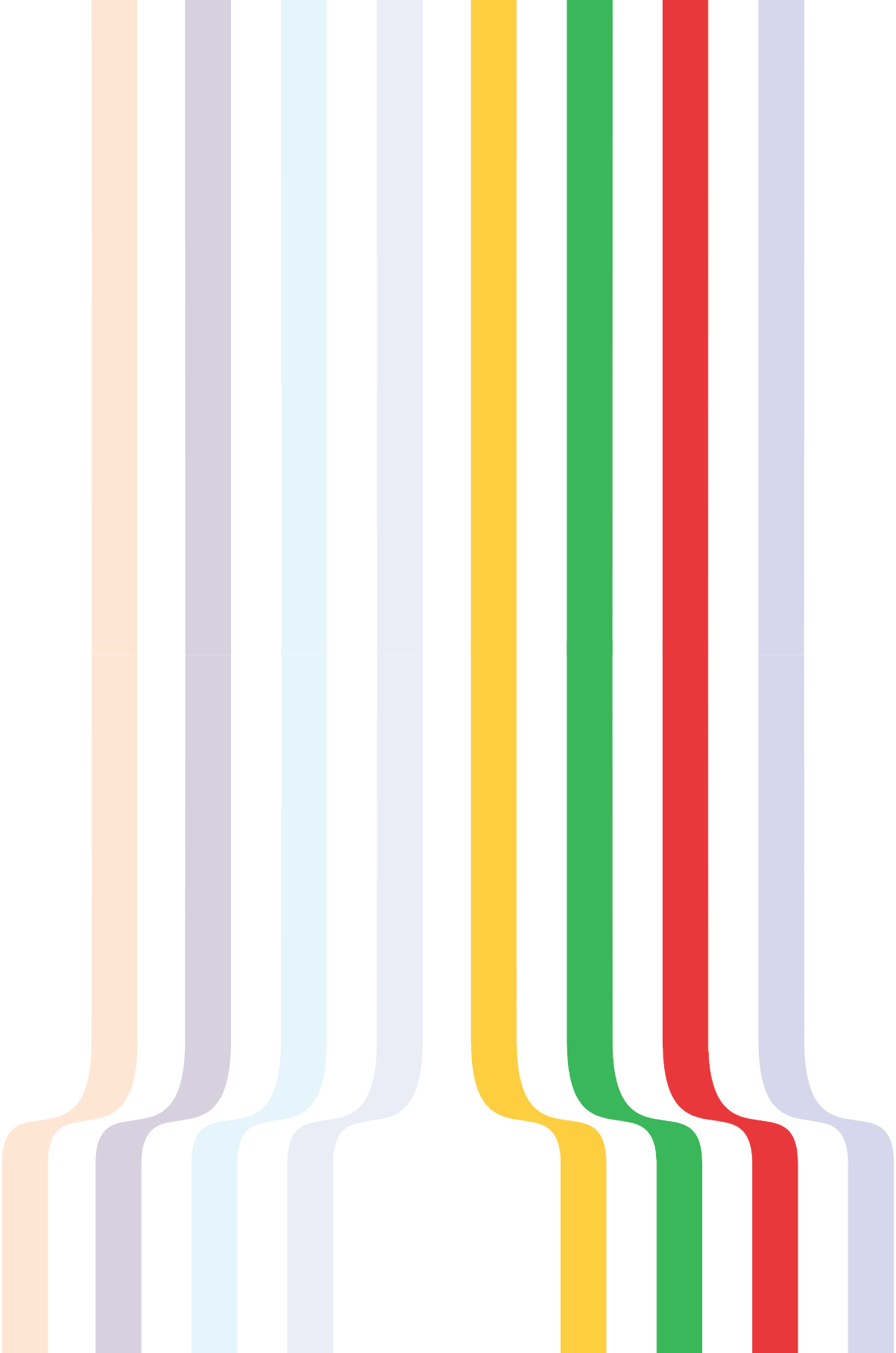
[a]Number of patients.
[b]Total number of patients of whom data was obtained.
[c]In 46 patients in whom variable could be obtained.
*p = 0.01.
SIRS, systemic inflammatory response syndrome.

Supplemental Table 6. Occurrence of hernia-related complications and subsequent management in patients that received conservative therapy at baseline

Patient	Complication (*n*=15)	Treatment
1	Obstruction with respiratory failure	Deceased from complication in combination with extensive comorbidity
2	Recurrent episodes of strangulation	Endoscopic desufflation followed by elective surgery
3	Gastrointestinal bleeding	Elective surgery
4	Volvulus with ischemia	Endoscopic desufflation followed by elective surgery
5	Volvulus	Conservative
6	Gastrointestinal bleeding	Conservative
7	Gastrointestinal bleeding	Conservative
8	Gastrointestinal bleeding	Conservative
9	Gastrointestinal bleeding	Conservative
10	Strangulation with perforation	Emergency surgery, deceased after surgery due to septic shock
11	Gastric bleeding	Deceased from complication in combination with extensive comorbidity
12	Obstruction	Elective surgery
13	Gastric perforation due to gastric ulcer	Emergency surgery
14	Volvulus and respiratory failure	Endoscopic desufflation
15	Volvulus	Conservative

PART II

ACHALASIA



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7

European guidelines on achalasia: United European Gastroenterology and European Society of Neurogastroenterology and Motility recommendations

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ABSTRACT

Background

Achalasia is a primary motor disorder of the esophagus characterized by absence of peristalsis and insufficient lower esophageal sphincter relaxation. With new advances and developments in achalasia management, there is an increasing demand for comprehensive evidence-based guidelines to assist clinicians in achalasia patient care.

Methods

Guidelines were established by a working group of representatives from United European Gastroenterology, European Society of Neurogastroenterology and Motility, European Society of Gastrointestinal and Abdominal Radiology and the European Association of Endoscopic Surgery in accordance with the Appraisal of Guidelines for Research and Evaluation II instrument. A systematic review of the literature was performed, and the certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation methodology. Recommendations were voted upon using a nominal group technique.

Results

These guidelines focus on the definition of achalasia, treatment aims, diagnostic tests, medical, endoscopic and surgical therapy, management of treatment failure, follow-up and esophageal cancer risk.

Conclusions

These multidisciplinary guidelines provide a comprehensive evidence-based framework with recommendations on the diagnosis, treatment and follow-up of adult achalasia patients.

INTRODUCTION

Achalasia is a primary motility disorder in which insufficient relaxation of the lower esophageal sphincter (LES) and absent peristalsis result in stasis of ingested foods, subsequently leading to esophageal symptoms of dysphagia, regurgitation, chest pain or weight loss.[1] Achalasia occurs as an effect of the destruction of enteric neurons controlling the LES and esophageal body musculature by an unknown cause, most likely inflammatory. Idiopathic achalasia is a rare disease and affects individuals of both sexes and all ages. The annual incidence is estimated between 1.07 and 2.2 cases per 100,000 individuals, with prevalence rates estimated between 10 and 15.7 per 100,000 individuals.[2–4]

A diagnosis of achalasia should be considered when patients present with dysphagia in combination with other esophageal symptoms and when upper endoscopy has ruled out other disorders. Barium esophagogram may reveal a classic 'bird's beak' sign, esophageal dilation or a corkscrew appearance. Esophageal manometry is the golden standard for the diagnosis of achalasia. Incomplete relaxation of the LES, reflected by an increased integrative relaxation pressure, in the absence of normal peristalsis, are the diagnostic hallmarks. The use of high-resolution manometry (HRM) has led to the subclassification of achalasia into three clinically relevant groups based on esophageal contractility patterns, as seen in **Table 1**.

The clinical care of patients with achalasia has changed significantly in the past decade under the influence of new developments such as HRM, per-oral endoscopic myotomy (POEM) and studies providing new insights regarding achalasia subtypes, cancer risk and followup. Given the substantial growth of knowledge in past years, there is need for comprehensive, evidence-based European guidelines covering all aspects of the disease. These multidisciplinary guidelines aim to provide an evidence-based framework with recommendations on the diagnosis, treatment and follow-up of adult achalasia patients. Chagas disease and achalasia secondary to other disorders, as can be seen after fundoplication, bariatric surgery, sarcoid infiltration, opiate usage or malignancy, are not covered by these guidelines. These guidelines are intended for clinicians involved in their management, including gastroenterologists, endoscopists, radiologists, gastrointestinal (GI) surgeons, dietitians and primary-care practitioners.

METHODOLOGY

The achalasia guidelines working group

Ten researchers and clinicians with recognized expertise in the field of clinical achalasia management were gathered (A.B., G.B., P.F., A.P., S.R., A.S., A.T., E.T., B.W. and G.Z.) on behalf of United European Gastroenterology (UEG), the European Society of Neurogastroenterology and Motility (ESNM), the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) and The European Association of Endoscopic Surgery (EAES) to form a guidelines expert working group. All concerned societies were contacted and asked to support the

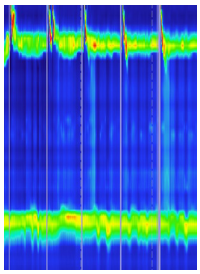
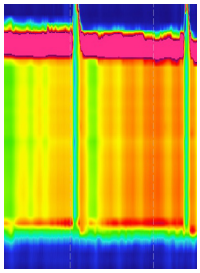
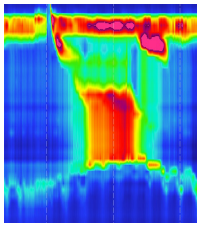
guidelines by appointing one or two representatives for the guidelines committee. First, the guidelines development team (R.O.N., A.B. and M.L.) drafted the guidelines protocol and the preliminary list of clinical topics to be covered by the guidelines. This list was circulated to a panel of achalasia patients. Based upon patients' interests, the final list of research questions was formatted into the PICO (patient, intervention, control, outcome) framework, and presented to all members of the guidelines working group at an initial meeting, which occurred on 23 October at UEG Week 2018. All working group members were assigned to one of the subgroups (diagnosis, treatment or follow-up) and were responsible for the elaboration of one or multiple research questions. Results of the search strategies and Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessments were first discussed in conference calls by each group and checked again for completeness, after which these documents were updated and subsequently sent to the entire group in advance of a face-to-face consensus meeting.

From assessment of evidence to recommendation

An electronic literature search was performed on 18 October 2018 using MEDLINE, EMBASE (accessed via Ovid), The Cochrane Database of Systematic Reviews (The Cochrane Library) and the Cochrane Central Register of Controlled Trials (CENTRAL) without restrictions of language or publication year. The search strategy and the process of study selection categorized per research question can be found in **Supplemental Tables 1, 2 and Supplemental Figure 1**. Risk of bias was assessed using the appropriate study-design specific tools (Online Appendix B). The certainty of evidence was assessed using the GRADE methodology (www.gradeworkinggroup.org) and, for each outcome, graded into four levels: high, moderate, low or very low quality (**Table 2**). Based on the certainty of evidence and the balance between desirable and undesirable outcomes, patient values and preferences, applicability, feasibility, equity and costs/resources, recommendations were categorized into four final categories (strong or conditional recommendations in favor of or against an intervention), as proposed by GRADE (**Table 3**). In case of insufficient or limited evidence, research questions were answered by and classified as 'expert opinion'. The results of data extraction, the risk of bias and quality of the evidence assessments are presented in Online Appendices C and D.

In order to establish consensus-based recommendations, a second physical meeting was organized in Amsterdam, The Netherlands, on 11 April 2019. GRADE assessments and recommendations were presented and discussed. Voting was conducted according to the nominal group technique and based upon a six-point Likert scale (1=strongly disagree; 2=mostly disagree; 3=somewhat disagree; 4=somewhat agree; 5=mostly agree; 6=strongly agree). A recommendation was approved if >75% of the members agreed (reflected by a Likert score of 4–6).

Table 1. Manometric subtypes of achalasia

Type I	Classic achalasia	Median IRP > cut-off[a] 100% failed peristalsis	
Type II	Achalasia with esophageal compression	Median IRP > cut-off[a] 100% failed peristalsis 20% pan-esophageal pressurization	
Type III	Spastic achalasia	Median IRP > cut-off[a] No normal peristalsis 20% premature contraction with DCI >450	

[a]The cut-off for IRP is catheter-depending, varying between 15 and 28 mmHg.
DCI: distal contractile integral; IRP: integrated relaxation pressure.

Table 2. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) definitions of quality and certainty of the evidence

Certainty of evidence	Definition
High	We are very confident that the true effect lies close to the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low	Our confidence in the estimate is limited. The true effect may be substantially different from the estimate of effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Table 3. GRADE on strength of recommendation and guide to interpretation

Strength of recommendation	Wording in the guideline	For the patient	For the clinician
Strong	'We recommend. . .'	Most individuals in this situation would want the recommended course and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	'We suggest. . .'	The majority of individuals in this situation would want the suggested course, but many would not.	Different choices would be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.

RECOMMENDATIONS

Clinical questions formed the basis of the systematic literature reviews (Online Appendix C). The working group formulated 30 recommendations based on these reviews (**Table 4**).

Table 4. Summary of recommendations of the United European Gastroenterology Clinical Guidelines Committee for the diagnosis, management and follow-up of achalasia

Recommendations		Strength	Certainty of evidence	Voting
	Diagnosis			
1.1	Achalasia is a disorder characterized by insufficient LES relaxation and absent peristalsis. It is usually primary (idiopathic) but can be secondary to other conditions that affect esophageal function. In idiopathic achalasia, the enteric neurons controlling the LES and esophageal body musculature are affected by an unknown cause, most likely inflammatory.	Expert opinion	-	100%
1.2	We recommend using high-resolution manometry (with topographical pressure presentation) to diagnose achalasia in adult patients with suspected achalasia.	Strong	Moderate	100%
1.3	We suggest using a barium esophagram to diagnose achalasia if manometry is unavailable, although it is less sensitive than esophageal manometry. The working group suggests using TBE, if available, over standard barium esophagram.	Conditional	Moderate	100%
1.4	We suggest against making the diagnosis of achalasia solely based on impaired EGJ distensibility as measured with impedance planimetry.	Expert opinion	-	100%
1.5	(a) We suggest against making the diagnosis of achalasia solely based on endoscopy.	Expert opinion	-	100%
	(b) We suggest performing endoscopy in all patients with symptoms suggestive of achalasia to exclude other diseases.	Expert opinion	-	77.8%
1.6	We suggest additional testing using CT or endoscopic ultrasound only in those achalasia patients suspected of malignant pseudo-achalasia. Multiple recognized risk factors for malignant pseudo-achalasia, for example >55 years old, duration of symptoms <12 months, weight loss >10 kg, severe difficulty passing the LES with a scope may prompt further imaging.	Conditional	Low	100%

Table continues on next page

Table 4 continued

	Recommendations	Strength	Certainty of evidence	Voting
	Diagnosis			
1.7	We suggest providing the patient with the following information on the disease and the treatment: Information on the disease: - normal function of esophagus; - rare condition that affects the neurons, leads to LES dysrelaxation and absent peristalsis, exact cause not known; - no increased chance of disease in siblings; - what might happen if left untreated; - no progression to other organs; - small increased risk of cancer. Information on treatment options: - explanation of all treatment options, choice of treatment is based upon shared decision making; - treatment is not curative but does improve symptoms; - risk of complications; - risk of reflux; - efficacy of treatments.	Expert opinion	-	100%
	Treatment			
2.1	(a) We suggest that in the treatment of achalasia, symptom relief should be regarded as the primary aim.	Expert opinion	-	100%
	(b) We suggest that improvement of objectively measured esophageal emptying on barium esophagram should be regarded as an important additional treatment aim.	Expert opinion	-	100%
2.2	We suggest against the use of calcium blockers, phosphodiesterase inhibitors or nitrates for the treatment of achalasia.	Expert opinion	-	100%
2.3	BTX therapy can be considered an effective and safe therapy for short-term symptom relief in esophageal achalasia.	Conditional	Moderate	88.9%
2.4	Graded pneumatic dilatation is an effective and relatively safe treatment for esophageal achalasia.	Strong	High	100%
2.5	POEM is an effective and relatively safe treatment for achalasia.	Strong	High	100%
2.6	LHM combined with an anti-reflux procedure is an effective and relatively safe therapy for achalasia.	Strong	High	100%
2.7	We suggest taking age and manometric subtype into account when selecting a therapeutic strategy.	Conditional	Moderate	100%
2.8	(a) Treatment decisions in achalasia should be made based on patient-specific characteristics, patient preference, possible side effects and/or complications and a center's expertise. Overall, graded repetitive PD, LHM and POEM have comparable efficacy.	Strong	Moderate	100%
	(b) BTX should be reserved for patients who are unfit for more invasive treatments, or in whom a more definite treatment needs to be deferred.	Conditional	Moderate	100%

Table 4 continued

	Recommendations	Strength	Certainty of evidence	Voting
2.9	We suggest treating recurrent or persistent dysphagia after LHM with PD, POEM or redo surgery.	Conditional	Very low	100%
2.10	We suggest treating recurrent or persistent dysphagia after POEM with either re-POEM, LHM or PD.	Conditional	Very low	100%
2.11	Esophagectomy should be considered the last resort to treat achalasia, after all other treatments have been considered.	Expert opinion	-	100%
2.12	We suggest against esophageal stents and intrasphincteric injection of sclerosing agents in the treatment of achalasia.	Expert opinion	-	100%
	Follow-up			
3.1	(a) Patients with recurrent or persistent dysphagia after initial treatment should undergo repeat evaluation with TBE with or without esophageal manometry.	Expert opinion	-	100%
	(b) Repeat endoscopy should be considered in patients with recurrent dysphagia.	Expert opinion	-	100%
3.2	(a) In patients with persistent or recurrent chest pain, inappropriate emptying due to ineffective initial treatment or recurrent disease should be excluded by TBE with or without esophageal manometry. For type III achalasia, we suggest a repeat HRM to exclude or confirm persistent spastic contractions.	Expert opinion	-	100%
	(b) If there is no evidence of impaired esophageal emptying, empirical treatment with PPI, endoscopy and/or 24-hour pH-(impedance)metry can be considered.	Expert opinion	-	100%
3.3	(a) We suggest follow-up endoscopy to screen for GERD in patients treated with myotomy without anti-reflux procedure.	Expert opinion	-	100%
	(b) In case of reflux symptoms in the absence of reflux esophagitis, TBE, empiric PPI therapy and/or 24-hour esophageal pH-(impedance) monitoring can be considered.	Expert opinion	-	100%
	(c) PPI are the first-line treatment of GERD after achalasia treatment. We recommend lifelong PPI therapy in patients with esophagitis > grade A (LA classification).	Expert opinion	-	100%
3.4	We suggest against performing systematic screening for dysplasia and carcinoma. However, the threshold of upper GI endoscopy should be low in patients with recurrent symptoms and long-standing achalasia.	Conditional	Low	100%

LES: lower esophageal sphincter; TBE: timed barium esophagram; EGJ: esophago-gastric junction; CT: computed tomography; BTX: botulinum toxin; POEM: per-oral endoscopic myotomy; LHM: laparoscopic Heller myotomy; PD: pneumatic dilation: PPI: proton pump inhibitors; GERD: Gastroesophageal reflux disease; GI: gastrointestinal.

1. ACHALASIA DIAGNOSIS

1.1 What is the current definition of achalasia?

Recommendation 1.1

Achalasia is a disorder characterized by insufficient LES relaxation and absent peristalsis. It is usually primary (idiopathic) but can be secondary to other conditions that affect esophageal function. In idiopathic achalasia, the enteric neurons controlling the LES and esophageal body musculature are affected by an unknown cause, most likely inflammatory.
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 100%; A+, 0%; A, 0%; D 0%; D+, 0%; D++, 0%)

1.2 What is the value of HRM and conventional manometry in achalasia diagnosis?

The diagnosis of achalasia requires not only impaired esophago-gastric junction (EGJ) relaxation, but also absent or abnormal peristalsis. Therefore, esophageal manometry is considered as being the gold standard for the diagnosis of achalasia, as it evaluates both pressures of the LES and contractility of the esophageal body. Worldwide, HRM, usually defined as manometry carried out with a catheter with at least 21 pressure sensors spaced at 1-cm intervals,[5] is rapidly replacing conventional manometry. The generally perceived advantages of HRM over conventional manometry are that positioning of the catheter is less critical and that interpretation of the recorded pressures, displayed in the form of topographical color-coded plots, is more intuitive.

In four of the five included studies, the diagnosis of achalasia was made with HRM more often than with conventional manometry.[6–9] However, one may argue that a higher rate of achalasia diagnosis with HRM does not prove that HRM is better than conventional manometry; HRM might also lead to more false-positive findings. The only prospective randomized trial that compared HRM and conventional manometry[9] had the additional advantage of defining the clinical outcome after six months as the gold standard, and found a superior sensitivity of HRM for the diagnosis of achalasia to that of conventional manometry (93% vs. 78%). The specificities of both tests were equal (100%).[9]

In two studies, the diagnostic values of imaging techniques were compared to manometry.[10,11] The results of these two studies lend some support to the notion that manometry rather than imaging is the gold standard for the diagnosis of achalasia.

Recommendation 1.2

We recommend using HRM (with topographical pressure presentation) to diagnose achalasia in adult patients with suspected achalasia.
Strong recommendation, moderate certainty of evidence
Consensus: 100% agree (Vote: A++, 66.7%; A+, 33.3%; A, 0%; D 0%; D+, 0%; D++, 0%)

1.3 What is the value of (timed) barium swallow studies in achalasia diagnosis?

The barium esophagram is generally seen as a valuable and complementary, but relatively insensitive, diagnostic test. One study evaluated the diagnostic value of barium esophagraphy in comparison to HRM and found a high sensitivity but poor specificity for detecting dysmotility. The authors concluded that barium swallow studies accurately rule out achalasia-related dysmotility but are not very helpful in diagnosing other causes of dysmotility.[12] Two studies comparing barium esophagraphy with conventional manometry found sensitivities for achalasia diagnosis between 58% and 75%.[11,13] However, as the positive predictive accuracy was 96%, the authors concluded that the barium esophagram is a useful tool in achalasia diagnosis.[11] Similar sensitivity and specificity rates were obtained in another study comparing barium swallow studies with HRM; the diagnostic sensitivity, specificity and accuracy of the barium esophagram were 78%, 88% and 83%, respectively.[14] Consequently, it may be concluded that diagnosing achalasia by using barium esophagram alone has a limited yield. The technique of timed barium esophagram (TBE) is similar to the usual barium swallow study but uses set time intervals (one, two and five minutes) after ingestion of a fixed barium suspension to measure the height and width of the barium column in order to assess esophageal emptying more objectively (**Figure 1**).[15] Because of this advantage, TBE is generally preferred over a standard barium esophagram. One study compared TBE to HRM, and found a sensitivity of 85% and specificity of 86%.[15]

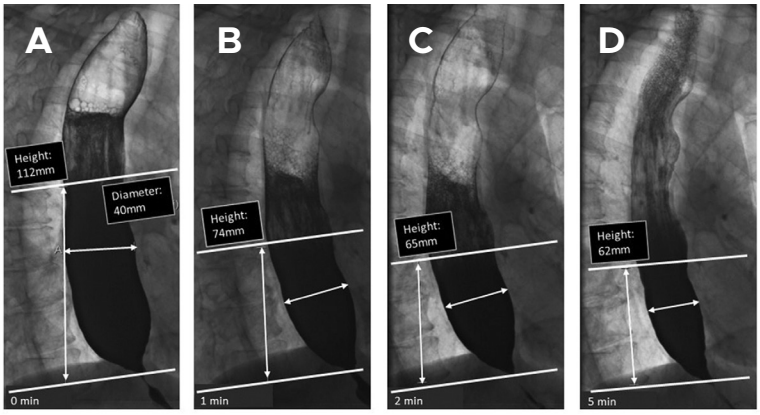


Figure 1. Interpretation of timed barium esophagram. Radiographs taken 0, 1, 2 and 5 minutes in left posterior oblique position after ingestion of 100 to 200 mL low-density barium suspension in an achalasia patient. Measurement of height and width of barium column, measured from the esophagogastric junction to the barium-foam interface. Barium height of >5 cm at 1 min and >2 cm at 5 min are suggestive of achalasia.

Recommendation 1.3

We suggest using a barium esophagram to diagnose achalasia if manometry is unavailable, although it is less sensitive than esophageal manometry. The working group suggests using TBE, if available, over standard barium esophagram.
Conditional recommendation, moderate certainty of evidence
Consensus: 100% agree (Vote: A++, 88.9%; A+, 11.1%; A, 0%; D 0%; D+, 0%; D++, 0%)

1.4 What is the value of esophageal impedance planimetry in the diagnosis of achalasia?

Esophageal impedance planimetry is a technique in which the cross-sectional area of the esophagus is simultaneously measured at multiple levels using a saline-filled cylindrical bag containing an array of impedance electrodes.[6] The commercially available device for endoluminal impedance planimetry is known as Endoflip®.

Studies using impedance planimetry have consistently demonstrated that the distensibility of the EGJ is reduced in untreated achalasia compared to healthy controls.[16–19] A systematic review identified six studies with data on EGJ distensibility in untreated achalasia patients (*N* = 154) and five studies with data in healthy subjects (*N* = 98), and found that at 40mL distension, there was a clear difference between the two groups (point estimates <1.6 mm^2/mmHg and >2.7 mm^2/mmHg in patients and controls, respectively).[20]

However, in order to distinguish achalasia from EGJ outflow obstruction, information about the motility of the tubular esophagus is required, which is not provided by impedance planimetry measurement. Recent studies indicate that dynamic impedance planimetry can also provide information on peristalsis.[21,22] However, this technique assesses distension- rather than swallow-induced contractions, and requires sedation. Furthermore, high-quality diagnostic studies comparing impedance planimetry with the gold standard HRM are not available yet. In line with this, one recommendation from a recent American Gastroenterological Association clinical practice update on functional lumen imaging is that clinicians should not make a diagnosis of achalasia based on impedance planimetry alone.[23]

There are data to suggest that impedance planimetry may be used as an additional tool to diagnose achalasia in patients who do not meet the manometric criteria (Chicago 3.0) for achalasia. In 13 patients with symptoms and signs of achalasia but with manometrically normal integrated relaxation pressure (IRP), EGJ distensibility was below the lower limit of normal. Treating these patients as if the diagnosis was achalasia resulted in a decrease in symptoms.[24] This observation suggests that impedance planimetry may be a useful complementary diagnostic tool for the diagnosis of achalasia in a subset of patients with a low IRP.

Recommendation 1.4

We suggest against making the diagnosis of achalasia solely based on impaired EGJ distensibility as measured with impedance planimetry.
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 100%; A+, 0%; A, 0%; D 0%; D+, 0%; D++, 0%)

1.5 What is the value of endoscopy in achalasia diagnosis?

Thorough endoscopic evaluation of the EGJ and gastric cardia is recommended in all patients with symptoms suggestive of achalasia in order to exclude other diseases, especially to rule out malignancies. However, the value of endoscopy in achalasia diagnosis is relatively low. Depending on the stage of disease, endoscopic evaluation can suggest a diagnosis of achalasia in 30–50% of patients. Achalasia diagnosis can easily be missed, as endoscopic abnormalities are uncommon in early-stage achalasia.[25–27] In more advanced stages, a diagnosis of achalasia is supported by endoscopic findings such as an esophageal dilatation with axis deviation and tortuosity and retained saliva and food in the esophagus.[28–30]

Recommendation 1.5

(a) We suggest against making the diagnosis of achalasia solely based on endoscopy.
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 100%; A+, 0%; A, 0%; D 0%;D+, 0%; D++, 0%)

(b) We suggest performing endoscopy in all patients with symptoms suggestive of achalasia to exclude other diseases.
Expert opinion recommendation
Consensus: 77.8% agree (Vote: A++, 77.8%; A+, 0%; A, 0%; D 0%; D+, 22.2%; D++, 0%)

1.6 In which patients should additional diagnostic tests be performed in order to exclude pseudo-achalasia?

Malignant pseudo-achalasia is a condition in which a patient is initially diagnosed with achalasia, and sometimes even treated for achalasia, but is later found to have an underlying malignancy as the primary cause. This can occur in a submucosally growing adenocarcinoma of the cardia, locally advanced pancreatic cancer, submucosal metastases or anti-Hu-producing carcinomas (typically small-cell lung carcinomas).[31] Certainly not all patients diagnosed with achalasia should undergo additional testing in the form of a computed tomography (CT) scan or endoscopic ultrasound to rule out malignancy. However, valuable time is missed if malignancy is not detected at an early stage. Only two studies have addressed the issue of how to identify patients with malignant pseudo-achalasia.[32,33] Both case-control studies identified the same differences between patients with primary achalasia and patients with malignant pseudo-achalasia: relatively short duration of symptoms, considerable weight loss and older age. The study by Ponds *et al.* also identified difficulty introducing the endoscope in the stomach, as mentioned by the endoscopist, as a risk factor. A model was produced

in which the presence of fewer than two risk factors did not result in increased risk for malignancy, while risk increased with the presence of two or more risk factors. The authors recommend additional testing in these patients.

Recommendation 1.6

We suggest additional testing using CT or endoscopic ultrasound only in those achalasia patients suspected of malignant pseudo-achalasia. Multiple recognized risk factors for malignant pseudo-achalasia, for example >55 years of age, duration of symptoms <12 months, weight loss >10 kg, severe difficulty passing the LES with a scope, may prompt further imaging.
Conditional recommendation, low certainty of evidence
Consensus: 100% agree (Vote: A++, 66.7%; A22.2%; A, 11.1%; D 0%; D+, 0%; D++, 0%)

1.7 What information should the newly diagnosed patient receive?

We recommend providing the patient with information on the disease and the treatment given in **Table 1.7.1**.

Table 1.7.1 Information the newly diagnosed achalasia patient should receive.

Information on the disease:
- normal function of the esophagus;
- rare condition that affects the neurons, leads to LES dysrelaxation and absent peristalsis, exact cause not known;
- no increased chance of disease in siblings;
- what might happen if left untreated;
- no progression to other organs;
- small increased risk of cancer.

Information on treatment options:
- explanation of all treatment options, choice of treatment is based upon shared-decision making;
- treatment is not curative but does improve symptoms;
- risk of complications;
- risk of reflux;
- efficacy of treatments.

Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 100%; A+, 0%; A, 0%; D 0%; D+, 0%; D++, 0%)

ACHALASIA TREATMENT

2.1 What should we aim for when treating achalasia patients?

Treatment can be considered for reducing symptoms and consequently improving quality of life. As the evidence for the use of standardized questionnaires in the clinical setting is limited, a thorough clinical assessment of esophageal symptoms before and after therapy should be used to evaluate treatment success. Second, treatment might prevent progression to end-stage disease and occurrence of late complications, such as aspiration and carcinogenesis. However, data on the natural history of disease to support this are scarce. There are series showing that if patients remain untreated, esophageal distension progresses over a period of

many years.[34,35] There is some indirect evidence that treatment can prevent progression of the disease. In a study evaluating patients treated with pneumatic dilation (PD), the persistence of esophageal stasis on TBE was associated with progressive esophageal dilatation of 0.5 cm in a two-year period, whereas successful PD (no stasis on TBE) was not.[36] Additionally, several surgical studies showed that treatment directed to LES pressure is less effective in patients with late-stage disease and a decompensated esophagus.[37–39] In summary, there is some indirect evidence that adequate treatment might reduce the risk of progressive esophageal dilation in patients with achalasia, potentially preventing a state of gross esophageal dilation, which in turn is associated with a poor outcome. In addition to the amelioration of symptoms, improvement of objectively measured esophageal emptying should therefore be regarded as an important additional treatment aim.

Recommendation 2.1

(a) We suggest that in the treatment of achalasia, symptom relief should be regarded as the primary treatment aim.
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 100%; A+, 0%; A, 0%; D 0%; D+, 0%; D++, 0%)

(b) We suggest that improvement of objectively measured esophageal emptying on barium esophagram should be regarded as an important additional treatment aim.
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 66.7%; A22.2%; A, 11.1%; D 0%; D+, 0%; D++, 0%)

2.2 What is the role of oral pharmacological therapy in achalasia?

There is no convincing evidence that treatment with smooth-muscle relaxants (calcium blockers, phosphodiesterase inhibitors or nitrates) provides symptomatic relief in adults with achalasia. The table presented in Online Appendix C summarizes the available literature. None of the studies is of sufficiently high quality, has sufficient sample size or measured adequate end points to answer this question.[40–46] Treatment with smooth-muscle relaxants can cause side effects and is therefore not recommended. It should certainly not delay an effective endoscopic or surgical treatment. Whether chest pain that is presumed to be due to spastic contractions can be relieved with medical therapy will be discussed in question 3.2.

Recommendation 2.2

We suggest against the use of calcium blockers, phosphodiesterase inhibitors or nitrates for the treatment of achalasia.
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 66.7%; A+, 33.3%; A, 0%; D 0%; D+, 0%; D++, 0%)

2.3 What is the comparative therapeutic efficacy and safety of endoscopic botulinum toxin injection in the treatment of achalasia?

Endoscopic injection of botulinum toxin (BTX) in the LES has been compared to laparoscopic

Heller myotomy (LHM) or endoscopic PD in several randomized controlled trials (RCTs).[47–49] The results of these studies all point in the same direction: BTX injections result in a reduction in LES pressure, stasis and symptoms in the short term, but generally the disease symptoms and signs recur with time. PD and BTX treatment are equally effective in the short term, while PD is the more effective endoscopic treatment in the long term (more than six months). LHM and BTX treatment are equally effective at the short term; LHM is the more effective treatment in the long term (more than six months).

Recommendation 2.3

BTX therapy can be considered an effective and safe therapy for short-term symptom relief in esophageal achalasia.
Conditional recommendation, moderate certainty of evidence
Consensus: 88.9% agree (Vote: A++, 88.9%; A+, 0%; A, 0%; D, 11.1%; D+, 0%; D++, 0%)

2.4 What is the comparative therapeutic efficacy and safety of endoscopic dilation?

PD has been compared to endoscopic BTX injections in the LES, POEM and LHM. A factor of importance when comparing the different studies is the PD regimen followed, which varies widely. Broadly speaking, treatment regimens with multiple dilations performed in case of recurrent symptoms increase the efficacy. A single series of PDs is less efficacious than LHM or POEM, while there is no difference in safety between the two treatment groups.[50–53] In studies in which repeated dilation was allowed upon symptom recurrence, the efficacy of PD generally approached that of LHM at a similar safety profile.[54–58] Given the risk of perforation, it is always advisable to start with a 30-mm balloon in an untreated achalasia patient. A second dilation with a 35-mm balloon will prolong the time to recurrence.[54,59]

Recommendation 2.4

Graded PD is an effective and relatively safe treatment for esophageal achalasia.
Strong recommendation, high certainty of evidence
Consensus: 100% agree (Vote: A++, 100%; A+, 0%; A, 0%; D 0%; D+, 0%; D++, 0%)

2.5 What is the comparative therapeutic efficacy and safety of POEM?

POEM appears to be a safe treatment option with a low rate of serious adverse events.[50,60] Although no long-term (beyond two years) follow-up data are available yet, POEM appears to be equally effective as LHM. In a recently published multi-center RCT, treatment success rate (defined as a reduction in Eckardt score <3 and the absence of severe complications or need for retreatment) after two years of follow-up was significantly higher in patients treated with POEM compared to patients treated with PD.[50] In this study, patients assigned to the PD arm were treated with a single 30-mm dilation, and received a second dilation with a 35-mm balloon if still symptomatic (which was the case in 50/66 (76%) patients). Gastro-

esophageal reflux disease (GERD) occurs more frequently after POEM than after LMH or PD, but high grades of esophagitis are uncommon.[61,62] However, one should note that it is very challenging to objectify GERD in achalasia patients, as gastroesophageal acid reflux is hard to differentiate from fermentation due to stasis. Nevertheless, in patients with a high risk of post-procedure GERD who are unwilling to use proton pump inhibitor (PPI) therapy, LHM or PD might be preferred over POEM.

Recommendation 2.5

POEM is an effective and relatively safe treatment for esophageal achalasia.
Strong recommendation, high certainty of evidence
Consensus: 100% agree (Vote: A++, 100%; A+, 0%; A, 0%; D 0%; D+, 0%; D++, 0%)

2.6 What is the comparative therapeutic efficacy and safety of surgical myotomy?

During a surgical cardiomyotomy, the spastic LES is disrupted by cleaving the muscle layers of both the LES and cardia, allowing the passage of food. Nowadays, the procedure is typically performed laparoscopically and combined with a partial anti-reflux procedure (fundoplication). A complete 360° wrap should be avoided in achalasia patients in order to prevent worsening, rather than relieving, the dysphagia.[63] Six RCTs compared the efficacy of LHM versus PD (two of them reporting long-term results), and multiple meta-analyses were performed.[51–58,64,65] These studies report a similar outcome for LHM and PD when multiple sessions of graded dilations were allowed (sequential dilations). However, LHM performed better than two sessions of PD. The meta-analysis (where PD outcome was assessed independently of the number of PD sessions) was in favor of LHM. LHM was more effective than PD in type III achalasia in a subgroup analysis of the European Achalasia Trial. One RCT compared LHM to BTX injection and showed a better outcome for LHM after six months of follow-up after an initial similar response.[49] Only one RCT, comparing LHM and POEM, shows a similar symptomatic outcome for the two treatments after a follow-up of up to two years.[60] A meta-analysis focusing on risk of iatrogenic reflux after POEM versus LHM suggested the increased risk of GERD after POEM.[61]

Recommendation 2.6

LHM combined with an anti-reflux procedure is an effective and relatively safe therapy for achalasia.
Strong recommendation, high certainty of evidence
Consensus: 100% agree (Vote: A++, 100%; A+, 0%; A, 0%; D, 0%; D+, 0%; D++, 0%)

2.7 What are predictors of treatment outcome? How to choose initial treatment

In order to guide therapeutic decisions, it is useful to distinguish patient types that are likely to respond favorably to a certain therapy. Patient-specific factors such as age, sex and manometric type are commonly believed to be predictive of treatment outcome, with the

unfavorable effect of young age undoubtedly being the most frequently described example.[66–69] A recently published review systematically assessed 75 studies that investigated potential patient-specific predictors.[70] A total of 34 predictors were identified, but of all pretherapeutic factors, only age and manometric subtype were identified as important predictors with a strong level of cumulative evidence. A meta-analysis confirmed that older patients (>45 years) responded better to PD treatment than younger individuals. Manometric subtype 3 was associated with poor treatment outcome in general. Interestingly, of the 49 included studies that evaluated sex as potential predictor, 90% did not find an association between sex and treatment outcome, indicating that sex most likely is not of predictive value in clinical decision making. The predictive value of some of the studied factors, such as chest pain and symptom severity, remains unclear, as the total body of evidence was inconclusive or insufficient to draw firm conclusions. It is suggested that age and manometric subtype should be taken into account when selecting a therapeutic strategy, in conjunction with information on efficacy and safety of the individual procedures, patient preference and local expertise.

Recommendation 2.7

We suggest taking age and manometric subtype into account when selecting a therapeutic strategy.
Conditional recommendation, moderate certainty of evidence
Consensus: 100% agree (Vote: A++, 100%; A+, 0%; A, 0%; D, 0%; D+, 0%; D++, 0%)

2.8 Overall recommendations on treatment (comparative effectiveness and safety)

Based on the systematic reviews and GRADE assessments of research questions 2.3–2.7 combined, the working group proposes the following overall recommendations with regard to achalasia therapy:

Recommendation 2.8

(a) Treatment decisions in achalasia should be made based on patient-specific characteristics, the patient's preference, possible side effects and/or complications and a center's expertise. Overall, graded repetitive PD, LHM and POEM have comparable efficacy.
Strong recommendation, moderate certainty of evidence
Consensus: 100% agree (Vote: A++, 55.6%; A+, 44.4%; A, 0%; D 0%; D+, 0%; D++, 0%)

(b) BTX therapy should be reserved for patients who are too unfit for more invasive treatments, or in whom a more definite treatment needs to be deferred.
Conditional recommendation, moderate certainty of evidence
Consensus: 100% agree (Vote: A++, 100%; A+, 0%; A, 0%; D 0%; D+, 0%; D++, 0%)

2.9 How to treat recurrence post LHM

Minimally invasive surgical therapy in achalasia is effective in the majority of patients. However, symptom relapse occurs in 10–20% of patients in the long term.[55] No adequate prospective controlled trials have been conducted on management of failed LHM due to low

patient numbers. Current options for the treatment of LHM recurrence include endoscopic dilation, POEM or redo surgery. When no gross anatomic abnormalities are present, PD or POEM can be considered. Both procedures show equally modest efficacy rates, but PD is often regarded a less invasive first step.[71–79] In the event of recurrence due to a too tight or twisted fundoplication, or a more complex anatomy with esophageal distortion, fibrosis or a post-myotomy diverticulum, redo surgery may be considered. However, this is associated with a substantial risk of postoperative complications.[74,80–82]

Recommendation 2.9

We suggest treating recurrent or persistent dysphagia after LHM with PD, POEM or redo surgery.
Conditional recommendation, very low certainty of evidence
Consensus: 100% agree (Vote: A++, 22.2%; A+, 77.8%; A, 0%; D 0%; D+, 0%; D++, 0%)

2.10 How to treat recurrence post POEM

Although POEM has good to excellent efficacy rates, treatment failure with recurrent or persistent symptoms does occur.[50,62,83] In a recently published RCT comparing endoscopic myotomy with PD, the authors reported clinical failure in 8% of patients treated with POEM after two years of follow-up.[50] Data on the best therapeutic approach after POEM failure are limited. Two case series reported success rates of 80–100% after three months of follow-up in patients treated with re-POEM after initial failure.[84,85] Another study evaluating retreatment after POEM failure in 43 patients showed that retreatment with either LHM or re-POEM gives modest efficacy rates of 45% and 63%, respectively, whereas PD showed a poor efficacy of only 20%.[86] These results may indicate the superiority of both POEM and LHM compared to PD in the management of POEM failure. However, it must be noted that the data to support this are weak and based on case series only. Moreover, PD is feasible and available in many centres, and is considered to be less invasive than re-myotomy and can therefore not be omitted completely in the management of this patient group.

Recommendation 2.10

We suggest treating recurrent or persistent dysphagia after POEM with either re-POEM, LHM or PD.
Conditional recommendation, very low certainty of evidence
Consensus: 100% agree (Vote: A++, 77.8%; A+, 22.2%; A, 0%; D 0%; D+, 0%; D++, 0%)

2.11 What are the indications for esophagectomy?

Esophagectomy for achalasia is associated with a high risk of complications and mortality.[87,88] A systematic review of eight studies and 1307 patients who underwent esophagectomy reported a complication rate of 19–50% and a mortality rate of 0–3.8%.87 In a large series of more than 500 patients, esophagectomy was initially performed in <1% of the entire population, but ultimately 17% of patients required esophageal resection, particularly those who failed surgical treatment or those with end-stage achalasia, which is often associated with massive

esophageal dilatation and tortuosity.[82] In a report on 53 patients with end-stage achalasia who underwent esophageal resection, the indications were tortuous mega-esophagus (64%) or esophageal stricture formation due to reflux (7%).[89] Other indications for esophageal resection are the presence of high-grade dysplasia or cancer. Although in-hospital mortality after esophagectomy is lower in patients with achalasia than in patients with cancer (2.8% vs. 7.7%, respectively), it is still a substantial risk, especially as the indication for resection is not as strong as for malignant disease. Moreover, the overall postoperative complication rate is similar in both patient groups.[90] Hence, esophagectomy should be considered the last resort in end-stage achalasia, where disabling symptoms reoccur despite aggressive treatment.[91,92] On the other hand, as the risk and complexity of esophageal resection increases with the deterioration of a patient's condition and nutritional status, end-stage achalasia should be carefully followed up to identify promptly when esophagectomy is necessary.

Recommendation 2.11

Esophagectomy should be considered the last resort to treat achalasia, after all other treatments have been considered.
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 77.8%; A+, 22.2%; A, 0%; D 0%; D+, 0%; D++, 0%)

2.12 What is the role of alternative therapies in the treatment of achalasia?

Several studies have investigated the use of alternative therapies such as esophageal stents[93–101] and intrasphincteric injection with ethanolamine oleate in achalasia treatment.[102–105] Overall, there is no high-quality evidence to support that either of these therapies is effective for symptom relief in achalasia patients. Moreover, as occurrence of complications such as bleeding, stent migration or strictures are fairly common, use of these therapies is not recommended.

Recommendation 2.12

We suggest against esophageal stents and intrasphincteric injection of sclerosing agents in the treatment of achalasia.
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 100%; A+, 0%; A, 0%; D 0%; D+, 0%; D++, 0%)

3. ACHALASIA FOLLOW-UP

3.1 How to diagnose and manage recurrent or persistent dysphagia after treatment

Despite treatment, a proportion of patients will experience ongoing or recurrent symptoms that significantly impair quality of life.[86,106] In some cases, treatment does not lead to meaningful improvement in the first place (persistent symptoms). In others, a period of initial improvement

is followed by subsequent recurrence. In general terms, the former suggests that initial treatment was incomplete, whereas the latter can be due to a variety of causes. There is no universal definition of what constitutes persistence or recurrence of symptoms. In most trials, an Eckardt score of >3 or a <50% improvement in symptoms is regarded as treatment failure.[47,50,54,107–109] However, this fails to distinguish between dysphagia and alternative troublesome symptoms such as regurgitation or chest pain. Although dysphagia is the most common ongoing symptom after achalasia treatment,[86] the etiology may be different from that in the treatment-naive setting (see **Table 3.1.1**).

Given the wide variety of potential causes of recurrent dysphagia, it is critical to undertake a comprehensive evaluation using objective testing in order to determine the pathophysiology underpinning the recurrent symptoms, and thus select the appropriate treatment. Conversely, in selected cases of persistent dysphagia, where the diagnosis of achalasia is beyond doubt, it may be appropriate to proceed immediately to further treatment without repeat testing (e.g. POEM after failure to improve with PD).

Since the commonest causes of recurrent dysphagia are incomplete myotomy, post-treatment scarring and esophageal stasis due to aperistalsis and functional dysphagia, objective testing should be targeted at these conditions. TBE helps to determine if there is a persistent delay to esophageal emptying, but reports regarding its usefulness as a predictor of long-term treatment success are conflicting.[36,55,108] HRM provides additional information on LES pressure. Impedance planimetry might be a useful complementary tool to assess EGJ distensibility and determine treatment efficacy.[16,110] In patients with a suspicion of severe esophagitis, possible candida esophagitis or anatomic abnormalities endoscopy should be considered.

Table 3.1.1. Potential causes for persistent and recurrent dysphagia after initial treatment

Common
- Persistent EGJ non-relaxation (e.g. incomplete myotomy)
- Post-treatment esophageal fibrosis/scarring
- Excessively tight fundoplication post myotomy
- Gastroesophageal reflux (with or without esophagitis)
- Aperistalsis and esophageal stasis
- Functional dysphagia

Uncommon
- Development of malignant stricture
- Wrap migration after fundoplication and myotomy
- Benign stricture (e.g. from reflux)
- Extrinsic compression from hiatal hernia (paraesophageal) or post-treatment collection

Recommendation 3.1

(a) Patients with recurrent or persistent dysphagia after initial treatment should undergo repeat evaluation with TBE with or without esophageal manometry.
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 100%; A+, 0%; A, 0%; D 0%; D+, 0%; D++, 0%)

(b) Repeat endoscopy should be considered in patients with recurrent dysphagia.
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 66.7%; A+, 33.3%; A, 0%; D 0%; D+, 0%; D++, 0%)

3.2 How to diagnose and manage recurrent or persistent chest pain after treatment

Although chest pain is one of the main presenting symptoms of achalasia, its response to treatment is less well studied and remarkably underreported, most likely as dysphagia is considered the leading and most relevant symptom. Nevertheless, up to 64% of patients report chest pain, often occurring in the middle of the night (in 47% of patients with chest pain) and lasting from a few minutes to almost 24 hours.[111] In contrast to dysphagia, chest pain is more challenging to treat and represents a risk factor for unsatisfactory treatment results for both PD and LHM.[37,54,112] In approximately 19% of patients, chest pain is completely relieved following LHM, but in the remainder, chest pain persists, with an intensity that is less (73%), similar (21%) or even more severe (4%) than before surgery.[113] Comparable results have been reported for PD.[111] Of note, chest pain persists in these patients, even though dysphagia was successfully treated. In general, achalasia-associated chest pain seems to decrease with time, but complete disappearance is rather exceptional.[111]

The exact cause underlying (non-cardiac) chest pain remains unknown, and can be attributed to acid reflux, esophageal motor abnormalities or visceral hypersensitivity. However, as chest pain is also considered to result from esophageal distension as a result of incomplete emptying, treatment failure should first be excluded in patients with persistent or recurrent chest pain by performing esophageal manometry and TBE.

If manometry (IRP above cut-off; catheter-depending, varying between 15 and 28 mmHg)[114] or TBE barium column height of >5cm after 5 minutes are abnormal,[115] treatment should aim to normalize esophageal emptying. HRM also serves to exclude spastic contractions as cause of the pain. If there is no evidence indicating insufficient treatment, one can consider investigation for GERD as the trigger of chest pain using 24-hour pH (impedance) monitoring and treat accordingly.[116] Data demonstrating the effect of PPI on chest pain in achalasia are, however, lacking, and anecdotally the response to PPI is poor if there is chest pain without heartburn.

The management of achalasia patients with chest pain with no evidence of GERD and normal esophageal emptying/IRP remains a major challenge, mainly as there are no or only a limited

number of RCTs available. Hence, clinical decision making is mostly based on studies performed in patients with non-cardiac chest pain due to esophageal dysmotility. Potential options for medical treatment are smooth-muscle relaxants (nifedipine, nitrates, diltiazem), BTX injection or neuromodulators (imipramine, venlafaxine, sertraline).[116] However, the success rates are rather limited and/or the effect is short lasting (in the case of BTX). Of interest, evidence is accumulating that POEM might be effective in relieving chest pain in patients with achalasia and other primary esophageal motility disorders. Several case series evaluating patients with hypercontractile esophageal motility disorders and chest pain who were treated with POEM showed promising results.[117–120] However, as none of the studies were sham-controlled, patient numbers were small and lengths of follow-up relatively short, future controlled data with longer follow-up are needed to investigate the exact role of POEM for patients with chest pain after initial achalasia treatment.

Recommendation 3.2

(a) In patients with persistent or recurrent chest pain, inappropriate emptying due to ineffective initial treatment or recurrent disease should be excluded by TBE with or without esophageal manometry. For type III achalasia, we suggest a repeat HRM to exclude or confirm persistent spastic contractions.
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 88.9%; A+, 11.1%; A, 0%; D 0%; D+, 0%; D++, 0%)

(b) If there is no evidence of impaired esophageal emptying, empirical treatment with PPI, endoscopy and/or 24-hour pH (impedance) monitoring can be considered.
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 100%; A+, 0%; A, 0%; D 0%; D+, 0%; D++, 0%)

3.3 How to manage reflux disease after treatment

As the aim of achalasia treatment is to alleviate the EGJ obstruction, an expected side effect of treatment is the occurrence of GERD, usually defined in achalasia as the presence of reflux esophagitis or pathological acid exposure. Indeed, GERD is frequently observed after treatment (10–31% of cases after PD,[51–53,55,58,121] 5–35% after LHM[52,53,55,121–123] and up to 60% of patients after POEM[50,60,61,124–126]). GERD complications, including peptic stricture, Barrett's mucosa and esophageal adenocarcinoma (EA), have been reported after achalasia treatment.[124,126–130] Comparative studies demonstrated that the rate of GERD was similar after PD and LHM with fundoplication.[121] One study showed that LHM without lateral and posterior dissection might also achieve sufficient reflux control.[131] However, in other studies, the prevalence of GERD was significantly higher after POEM or LHM without fundoplication than after PD or LHM with fundoplication.[50,60,62,132] Therefore, systematic screening for GERD after achalasia treatment should be recommended if the risk for GERD is high. Moreover, due to the different GERD rates, the choice of achalasia treatment should take into account the risk of iatrogenic reflux disease. In line with this, empiric PPI therapy might be considered in patients who undergoing myotomy without an anti-reflux procedure.

GERD symptoms such as heartburn and regurgitation are not reliable to diagnose GERD in achalasia patients, especially as regurgitation is also a hallmark of achalasia and poor esophageal emptying. An upper endoscopy can reveal esophagitis and Barrett's mucosa as proof of GERD. Another way to diagnose GERD is 24-hour esophageal pH monitoring. The interpretation of this examination requires a careful review of pH tracings to eliminate periods of esophageal fermentation.[53] The correlation between esophageal symptoms and objective diagnosis of GERD (including esophagitis and esophageal acid exposure) is poor.[62,123,133–135] Upper GI endoscopy, TBE and 24-hour pH monitoring might be complementary.

So far, no study has clearly evaluated the management of GERD after achalasia treatment. Post-treatment GERD is usually treated successfully with PPI. The percentage of patients on PPI after achalasia treatment is up to 60%.[60,61,136–138] Few other GERD treatments have been proposed for refractory cases and presented only as case reports (redo fundoplication, Roux-en-Y gastric bypass, esophagectomy, transoral incisionless fundoplication).[89,139,140]

Recommendation 3.3

(a) We suggest follow-up endoscopy to screen for GERD in patients treated with myotomy without anti-reflux procedure.
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 44.4%; A+, 44.4%; A, 11.1%; D 0%; D+, 0%; D++, 0%)

(b) In case of reflux symptoms in the absence of reflux esophagitis, TBE, empiric PPI therapy and/or 24-hour esophageal pH-(impedance) monitoring can be considered.
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 77.8%; A+, 22.2%; A, 0%; D 0%; D+, 0%; D++, 0%)

(c) PPIs are the first-line treatment of GERD after achalasia treatment. We recommend lifelong PPI therapy in patients with esophagitis >grade A (LA classification).
Expert opinion recommendation
Consensus: 100% agree (Vote: A++, 33.3%; A+, 55.6%; A, 11.1%; D 0%; D+, 0%; D++, 0%)

3.4 Is surveillance endoscopy for dysplasia needed?

What is the incidence of esophageal cancer in achalasia patients? Achalasia is a risk factor for esophageal cancer. Poor esophageal clearance increases bacterial growth, chemical irritation and mucosal inflammation that can facilitate dysplastic changes of esophageal epithelial cells and result in squamous-cell carcinoma (SCC).[141] Furthermore, acid exposure secondary to reduction of EGJ pressure as a consequence of achalasia treatment may lead to Barrett's mucosa and esophageal adenocarcinoma (EA).[142]

The exact level of risk for esophageal cancer (SCC and EA) is controversial. Differences in study design (retrospective or prospective, length of Follow-up, number of patients, countries) might explain some of the observed differences. While the absolute risk of esophageal cancer is quite low in achalasia, the relative risk of cancer is higher in achalasia patients than in the

general population (risk ratio to develop EA and SCC in achalasia patients is 6.63 and 72.65, respectively).[143,144] Most of the cases of carcinoma are observed more than 10 years after symptom onset.[144,145] The type of treatment does not influence the risk of cancer,[130,146] but to date there are no longterm data following POEM. Cancer risk might be higher in males and in patients with Chagas disease.[130,146,147]

Screening practices differ among geographic regions (routine endoscopy vs. no endoscopy, screening intervals).[92,148] Chromoendoscopy with lugol was proposed to improve the detection rate of dysplastic lesion, but the yield was low and hampered by stratification risk.[145]

Finally, the cost efficacy of the screening has not been demonstrated; the low absolute risk of cancer and the difficulty of identifying pre-neoplastic lesions might explain the absence of the advantage of screening achalasia patients for esophageal cancer.

Recommendation 3.4

We suggest against performing systematic screening for dysplasia and carcinoma. However, the threshold of upper GI endoscopy should be low in patients with recurrent symptoms and longstanding achalasia.
Conditional recommendation, low certainty of evidence
Consensus: 100% agree (Vote: A++, 66.7%; A+, 33.3%; A, 0%; D 0%; D+, 0%; D++, 0%)

CONCLUSIONS AND FUTURE PERSPECTIVES

The ESNM/UEG guidelines on the management of achalasia are the result of an evidence-based approach and international and multidisciplinary efforts. These guidelines provide recommendations for key aspects of the diagnosis and management of achalasia, combined with comments based on the best available literature and the opinions of leading European achalasia experts. The main objectives of these guidelines are to reduce variation in practice and to improve patient outcomes across Europe. Consequently, thorough and extensive dissemination of these guidelines is needed to assure high compliance in clinical practice. Promotion of these guidelines as well as education play a key role in this regard. Future well-designed clinical trials should address the knowledge gaps and unmet needs that have arisen during the development of these guidelines.

AUTHOR CONTRIBUTIONS

RON and AB were responsible for drafting the guidelines protocol, coordinating the development of the guidelines and the initial list of research questions to be covered by the guidelines. RON and ML conducted the literature search and systematic selection of articles. Working group expert members (AB, GB, PF, AP, SR, AS, AT, ET, BW, GZ) systematically appraised the literature and assessed the evidence according to GRADE and drafted the statements. RON and ML provided methodological support. All expert members voted on the recommendations. RON and AB drafted the manuscript, which was reviewed, revised and approved by all authors.

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Supplemental Table 1. Overview of research questions with corresponding in- and exclusion criteria

Research questions		PICO (inclusion criteria)		Exclusion criteria	Included studies
Diagnosis					
1.1	What is the current definition of achalasia?	P I C O	Expert opinion	-	-
1.2	What is the value of HRM and conventional manometry in achalasia diagnosis?	P I C O	Adult patients with suspicion of achalasia High resolution manometry All other diagnostic tests Diagnostic accuracy (sensitivity, specificity) Secondary outcomes: Inter/intra observer agreement; learning curve	Exclusion criteria: studies that did not comply with PICO	Roman 2016; Carlson 2015; Grübel 2008; Clouse 2000; O'Rourke 2016; Soudagar 2012; Parkman 1996; Fox 2004
1.3	What is the value of (timed) barium swallow studies in achalasia diagnosis?	P I C O	Adult patients with suspicion of achalasia (timed) Barium swallow studies All other diagnostic tests Diagnostic accuracy (sensitivity, specificity) Secondary outcomes: Inter/intra observer agreement; learning curve	Exclusion criteria: studies that did not comply with PICO	Blonski 2018; El-Takli 2006; Parkman 1996; Stacher 1994; Singhal 2013; Füller 1999; Aronova 2017; Yamasaki 2018
1.4	What is the value of impedance planimetry (EndoFlip) in the diagnosis of achalasia?	P I C O	Adult patients with suspicion of achalasia Impedance planimetry (EndoFlip) All other diagnostic tests Diagnostic accuracy (sensitivity, specificity) Secondary outcomes: Inter/intra observer agreement; learning curve	Exclusion criteria: studies that did not comply with PICO	*No studies compared diagnostic accuracy of EndoFlip versus other techniques -> Expert opinion question
1.5	What is the value of endoscopy in achalasia diagnosis?	P I C O	Adult patients with suspicion of achalasia Upper endoscopy All other diagnostic tests Diagnostic accuracy (sensitivity, specificity) Secondary outcomes: Inter/intra observer agreement; learning curve	Exclusion criteria: studies that did not comply with PICO	*No studies compared diagnostic accuracy of Endoscopic versus other techniques -> Expert opinion question

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Research questions			PICO (inclusion criteria)	Exclusion criteria	Included studies
Diagnosis					
1.6	In what patient should we perform additional diagnostic tests to exclude pseudo-achalasia?	P I C O	Adult achalasia patients - - Prognostic clinical factors for pseudo-achalasia	Exclusion criteria: studies that did not comply with PICO, no clinical factors described, *n* < 10 patients	Ponds 2017; Rozman 1990
1.7	What information should the newly diagnosed patient receive?	P I C O	Expert opinion	-	-
Treatment					
2.1	What are the indications for treatment of achalasia and what should be strived for when treating patients with achalasia?	P I C O	Expert opinion	-	-
2.2	What is the role of oral pharmacological therapy in achalasia?	P I C O	Adult patients diagnosed with achalasia Botox injection (Other treatments) *Efficacy:* - Symptoms scores - Clinical remission (Y/N) - Need of re-intervention - QoL - LES pressure *Safety:* - Complications/(S)AEs - Occurrence of GERD	Only RCTs and/or SRs were included	Bortolotti 1981, Gelfond 1982, Nasrallah 1985, Marzio 1994, Bortolotti 2000; Eherer 2002; Wong 1987

Supplemental Table 1 continued

Research questions		PICO (inclusion criteria)	Exclusion criteria	Included studies
Treatment				
2.3	Botox therapy can be considered an effective and safe therapy for short-term symptom relief in esophageal achalasia (statement)	P Adult patients diagnosed with achalasia I Botox injection C (Other treatments) O *Efficacy:* - Symptoms scores - Clinical remission (Y/N) - Need of re-intervention - QoL - LES pressure *Safety:* - Complications/(S)AEs - Occurrence of GERD	Only RCTs and/or SRs were included	Leyden 2014 Pasricha 1995, Zaninotto 2004
2.4	What is the comparative therapeutic efficacy and safety of endoscopic dilatation?	P Adult patients diagnosed with achalasia I Botox injection C (Other treatments) O *Efficacy:* - Symptoms scores - Clinical remission (Y/N) - Need of re-intervention - QoL - LES pressure *Safety:* - Complications/(S)AEs - Occurrence of GERD	Only RCTs and/or SRs were included	Boeckxstaens 2011 & Moonen 2015; Kostic 2007 & Persson 2015; Hamdy 2015; Borges 2013; Novais 2010; Christoja 2016; Schoenberg 2013; Ponds 2019; Leyden 2014

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Research questions		PICO (inclusion criteria)		Exclusion criteria	Included studies
Treatment					
2.5	What is the comparative therapeutic efficacy and safety of per-oral endoscopic myotomy?	P I C O	Adult patients diagnosed with achalasia Botox injection (Other treatments) *Efficacy:* - Symptoms scores - Clinical remission (Y/N) - Need of re-intervention - QoL - LES pressure *Safety:* - Complications/(S)AEs - Occurrence of GERD	Only RCTs and/or SRs were included	Ponds 2019; Repici 2018; Schlottmann 2018; Werner 2018
2.6	What is the comparative therapeutic efficacy and safety of surgical myotomy?	P I C O	Adult patients diagnosed with achalasia Botox injection (Other treatments) *Efficacy:* - Symptoms scores - Clinical remission (Y/N) - Need of re-intervention - QoL - LES pressure *Safety:* - Complications/(S)AEs - Occurrence of GERD	Only RCTs and/or SRs were included	Boeckxstaens 2011 & moonen 2015; Kostic 2007 &Persson 2015; Hamdy 2015; Borges 2013; Novais 2010; Christoja 2016; Schoenberg 2013 ; Repici 2018; Schlottmann 2018, Werner 2018; Zaninotto
2.7	What are predictors for treatment outcome? How to choose initial treatment	P I C O	Achalasia patients - - Pre-treatment, patient-specific factors for treatment outcome	All studies (RCTs, prospective or retrospective observational) addressing the PICO question were included	Oude Nijhuis 2019

Supplemental Table 1 continued

Research questions			PICO (inclusion criteria)	Exclusion criteria	Included studies
Treatment					
2.8	What overall recommendations with regard to treatment can be made?	-	-	-	-
2.9	How to treat a post-Heller recurrence?	P I C O	Achalasia patients with recurrent symptoms after myotomy All therapies *Efficacy:* - Symptoms scores - Clinical remission/retreatment success - Need of secondary re-intervention - QoL *Safety:* - Complications/ S)AEs	RCTs, prospective observational studies and retrospective observational studies *n*>20 applicable to the PICO question were included	Zhou 2013; Onimaru 2013; Wood 2015; Zhang 2018; Tyberg 2018; Veenstra 2016; Fernandez-Ananin 2018
2.10	How to treat a post-POEM recurrence	P I C O	Achalasia patients with recurrent symptoms after myotomy All therapies *Efficacy:* - Symptoms scores - Clinical remission/retreatment success - Need of secondary re-intervention - QoL *Safety:* - Complications/ S)AEs	All studies (RCTs, prospective or retrospective observational) addressing the PICO question were included	van Hoeij 2018; Li 2016; Tyberg 2017
2.11	What are indications for esophagectomy?	P I C O	Expert opinion	-	-

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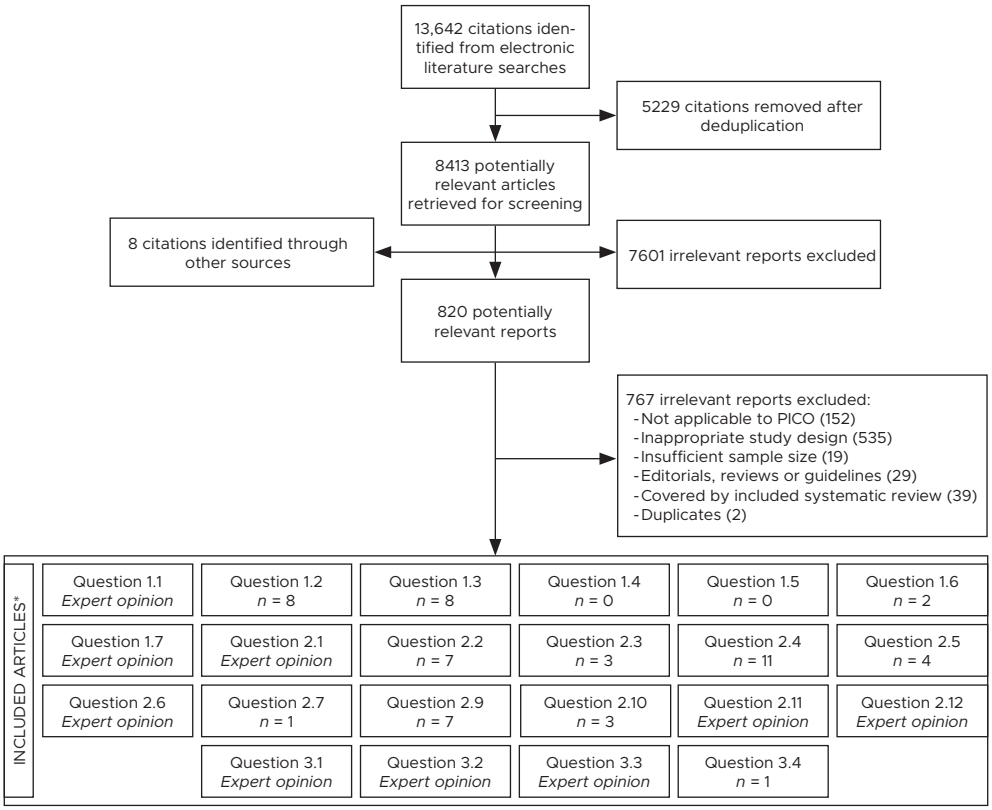
Research questions		PICO (inclusion criteria)		Exclusion criteria	Included studies
Treatment					
2.12	What is the role of alternative therapies such as esophageal stents and intrasphincteric injection of sclerosing agents in the treatment of achalasia?	P I C O	Expert opinion	-	-
Follow-up					
3.1	How to diagnose and manage recurrent or persistent dysphagia after treatment?	P I C O	Expert opinion	-	-
3.2	How to diagnose and manage recurrent or persistent chest pain after treatment?	P I C O	Expert opinion	-	-
3.3	How to manage reflux disease after treatment?	P I C O	Expert opinion	-	-
3.4	Is surveillance endoscopy for dysplasia needed? What is the incidence of esophageal cancer in achalasia patients?	P I C O	Treated achalasia patients - - Incidence of esophageal cancer, number needed to screen	Exclusion criteria: studies that did not comply with PICO	Tustumi 2017



Supplemental Figure 1. Process of study selection
*Included studies may overlap between PICO questions

Supplemental Table 2. Search strategy

MEDLINE (PubMed)		
("Esophageal Achalasia"(Mesh) OR achalasia*(tiab)) NOT ("Editorial" (Publication Type) OR "Letter" (Publication Type) OR "Comment" (Publication Type) OR "Case Reports" (Publication Type) OR letter(ti) OR case report*(ti))		
EMBASE (Ovid)		
1	esophagus achalasia/ or achalasia*.ti,ab,kw.	12397
2	limit 1 to conference abstract status	2421
3	1 not 2	9976 7
4	letter/ or editorial/ or case report/ or (letter* or case report*).ti. or editorial.ti,ab,kw.	3861827
5	3 not 4	7453
Cochrane Central Register of Controlled trials		
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Factors associated with achalasia treatment outcomes: systematic review and meta-analysis

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ABSTRACT

Background and Aims

Identification of factors associated with achalasia treatment outcome might help physicians select therapies based on patient characteristics. We performed a systematic review and meta-analysis to identify factors associated with treatment response.

Methods

We searched MEDLINE, EMBASE, and the Cochrane Library through February 21, 2019, for randomized controlled trials and cohort, case-control, and cross-sectional studies that reported patient-specific outcomes of treatment (botulinum toxin injection, pneumatic dilation, peroral endoscopic myotomy, or laparoscopic Heller myotomy). We assessed the methodologic quality of the included studies using the quality in prognosis studies tool. We planned qualitative and quantitative analyses.

Results

We analyzed data from 75 studies (8 randomized controlled trials, 27 prospective cohort studies, and 40 retrospective studies) on a total of 34 different factors associated with outcomes (3 demographic, 17 clinical, and 14 diagnostic factors). Qualitative assessment showed age, manometric subtype, and presence of a sigmoid-shaped esophagus as factors associated with outcomes of treatment for achalasia with a strong level of evidence. The cumulative evidence for the association with chest pain, symptom severity, and lower esophageal sphincter pressure was inconclusive. A meta-analysis confirmed that older age (mean difference, 7.9 y; 95% CI, 1.5–14.3 y) and manometric subtype 3 (odds ratio, 7.1; 95% CI, 4.1–12.4) were associated with clinical response.

Conclusions

In a systematic review and meta-analysis, we found age and manometric subtype to be associated with outcomes of treatment for achalasia. This information should be used to guide treatment decisions.

INTRODUCTION

Achalasia is a rare primary esophageal motor disorder in which ganglion cells in the myenteric plexus are affected, leading to aperistalsis or spastic contractions and an impaired relaxation of the lower esophageal sphincter (LES). Subsequent stasis of ingested foods results in symptoms such as dysphagia, regurgitation, respiratory symptoms, chest pain, and weight loss.[1] Because the neuronal loss is irreversible, current treatment of achalasia is limited to a reduction of symptoms. Clinical management may be challenging, especially because treatment success decreases in the long term, often leading to need for re-treatment.[2,3] Currently, there are several effective treatment modalities available that all aim to eliminate outflow resistance by disabling tonic contractions of the spastic LES.[4] Traditionally, endoscopic pneumatic dilatation (PD) and laparoscopic Heller myotomy (LHM) combined with a fundoplication are the treatments of choice and both have high success rates.[5] Endoscopic injection of botulin toxin is effective in the short term and is safe, and therefore is considered the first-line treatment for patients who are unfit for more invasive treatments. Other pharmacologic therapies include nitrates and calcium antagonists, but have limited clinical use because of more significant side effects.[1] As from 2011, the therapeutic arsenal has expanded with the introduction of peroral endoscopic myotomy (POEM). The first results of 2 randomized controlled trials comparing endoscopic myotomy with its laparoscopic equivalent and with pneumatic dilatation show a comparable efficacy rate and a superior safety profile.[6,7]

With several treatment options available, there is a growing demand for tailored treatment strategies for the individual achalasia patient. In the past years a variety of studies on clinical predictors of treatment outcome has been published, with factors such as sex and manometric subtype being the best known examples. The association between sex and treatment outcome has been reported mainly in the context of pneumatic dilatation. Patients with type III achalasia are known to respond relatively poorly to any form of treatment.[8–10] Although both factors have been described multiple times, their exact overall predictive value and corresponding lower level of underlying evidence remains insufficiently defined. As a consequence, no predictor has been incorporated in clinical guidelines. Moreover, identification of clinical predictors other than sex and subtype might guide individualized treatment strategies in achalasia patients and help reduce the risk of clinical failure, need for re-intervention, or risk of adverse events.

Accordingly, this study was conducted to systematically review the available literature on clinical predictors of response in achalasia treatment. We aimed to identify all patient-specific pretreatment factors for clinical response, appraise their predictive value, and discuss their potential use as predictors in clinical practice.

METHODS

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.[11] The study protocol was registered with the International Prospective Register of Systematic Reviews, registration number: CRD42019121741.

Literature Search

Electronic literature databases MEDLINE (PubMed), EMBASE (Ovid), and the Cochrane Library (Cochrane Central Register of Controlled Trials) were searched from inception to February 21, 2019. The full search strategy is detailed in **Supplemental Table 1**. Reference lists of key reports and review articles and meta-analyses were searched manually to identify additional studies.

Study Selection

All retrospective, prospective, controlled, and uncontrolled articles describing adult achalasia patients who were treated with either endoscopic botulinum toxin injection, pneumatic dilation, peroral endoscopic myotomy, or laparoscopic Heller myotomy, and that reported on patient-specific (clinical or diagnostic) pretreatment predictors, were assessed for eligibility. Decisions for inclusion of studies were made based on the predefined selection criteria shown in **Supplemental Table 2**. All non-English studies and studies published before 1990 were excluded, as well as studies with small study samples (retrospective, <50; prospective, <30). Two authors (R.O.N. and L.P.) independently assessed the titles and abstracts of all references retrieved by the literature search. Irrelevant studies and duplicates were removed. The remaining citations were retrieved in full text and screened independently by the same 2 reviewers. All available randomized controlled trials were assessed in full text to make sure that no potential high-quality evidence predictors were missed. Authors were contacted by email if the full text version could not be obtained. Disagreement regarding inclusion on abstract or full text level was resolved by consensus. Consensus was obtained by discussion and agreement among 3 authors (R.O.N., L.P, and A.B.). Screening was performed in Covidence (Veritas Health Innovation,Melbourne, Australia) and Endnote 17.7 (Clarivate Analytics, Philadelphia, PA).

Data Extraction and Assessment of Methodologic Quality

Two authors (R.O.N. and L.P.) independently extracted relevant data into a standardized spreadsheet (Excel Microsoft 2010 Redmond, WA). Extracted data from each study included the following: author, year of publication, country, study type, sample size, age, sex, period of recruitment and follow-up time, primary and secondary outcomes, number of patients previously treated, type of intervention and protocol followed, a complete list of all predictors explored, a list of all statistically significant predictors with predictive values, and cross references. Risk of bias (RoB) was rated on 6 domains using the Quality in Prognosis Studies

tool by both authors (R.O.N. and L.P.)[12] Because we wanted to provide a comprehensive overview of the cumulated strength of a certain predictor, we rated the overall risk of bias per study as well. Studies with a low risk of bias were defined as those studies in which at least 4 of 6 domains were rated as having a low risk of bias, and no domain was rated as having a high risk of bias. When more than 2 domains were rated as having a high risk of bias, or when 2 domains were rated as a high risk and 3 of the remaining domains were rated as moderate risk, the level of bias was rated as high. Any discrepancies were resolved through author consensus during both data collection and quality assessment by consultation of a third author (A.B.).

Statistical Analysis

To evaluate the effect of predictors, data were synthesized quantitatively, and, if possible, qualitatively. All assessed predictors are presented qualitatively, considering the strength and consistency of the results, using the following criteria (adapted from van Tulder *et al*[13]). First, a factor was classified as a predictor with a strong level of evidence if the majority (≥50%) of studies with at least multiple (≥2) high-quality studies showed a significant (and consistent) association. Second, a predictor with a moderate level of evidence was defined as having consistent findings in the majority (>50%) of multiple (≥2) studies, regardless of methodologic quality. Third, factors with limited or inconclusive evidence, or potential predictors, were defined as findings in 1 high-quality study or consistent findings in ≥3 low-quality studies. Fourth, a factor was classified as not predictive when ≥75% of the studies did not find an association.

Predictive factors that were classified as having a strong level of underlying evidence were selected for quantitative assessment. A meta-analysis was conducted if there were at least four compatible studies with a combined sample size ≥500. Between-study heterogeneity was assessed with the χ^2 test ($P < 0.10$ indicated the presence of heterogeneity, in which case a random-effects model was applied) and with the I^2 test (to assess the degree of heterogeneity). Bias was statistically tested using funnel plot asymmetry and a regression test. A P value less than 0.05 was considered statistically significant. All analyses were performed using R statistical software (version 3.5.1; R Core Team, Vienna, Austria), metafor package.

RESULTS

The initial electronic and manual reference search yielded 2356 citations after removal of duplicates. Non-applicable references (N = 2239) were excluded and 117 citations were screened in full text, of which 75 met the inclusion criteria (**Figure 1**). RoB assessments and characteristics of the included articles are presented in **Supplemental Table 3** and **Supplemental Table 4**, respectively. A list of excluded articles is provided in **Supplemental Table 5**. Ultimately, 8 randomized controlled trials, 27 prospective cohort studies, and 40 retrospective studies were included.

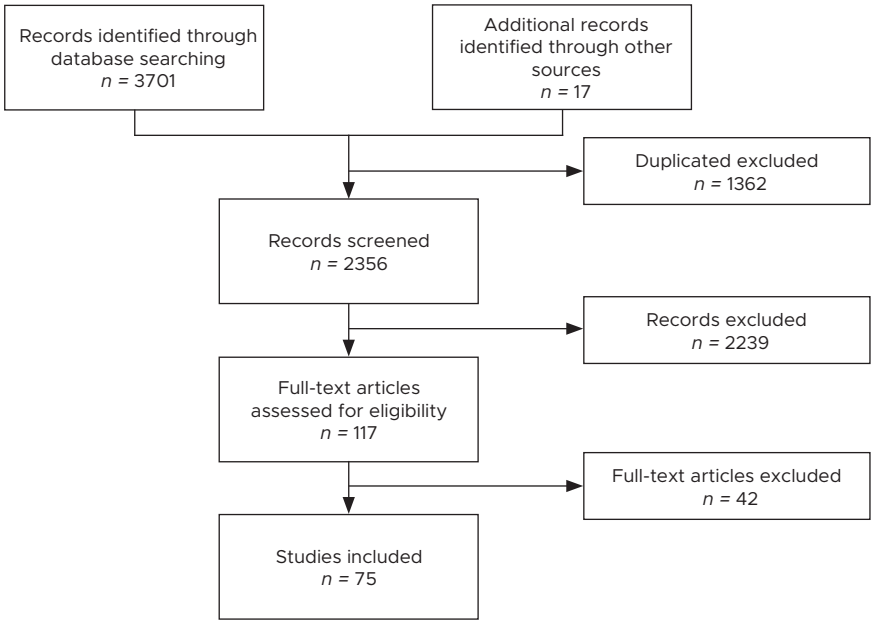


Figure 1. Flowchart of included studies

Predictors for Treatment Outcome

A total of 34 different potential prognostic factors were investigated in the 75 included studies: 3 demographic factors, 17 clinical factors, and 14 diagnostic factors. Of the included articles, 30 articles reported on PD, 33 reported on LHM, 14 studies described predictors of treatment outcome after POEM, and 7 studies reported on endoscopic Botox injection. All explored prognostic factors were categorized per treatment modality and are detailed in **Supplemental Table 6**. A comprehensive synthesis of the corresponding levels of evidence is shown in **Table 1**. Seven factors were analyzed only once. These factors were not included in this table because the level of evidence would by definition be low.

Demographic Predictors

Age

As shown in **Table 1**, age was examined most often as a predictive factor of treatment outcome; 48 of the 75 included articles assessed the predictive value of age, of which studies on pneumatic dilatation and laparoscopic Heller myotomy were most common. The majority of studies (*n* = 14, 8 low RoB studies and 6 moderate RoB studies) that looked into age as a predictive factor for response to pneumatic dilatation found a positive association. Eckardt *et al*[14] stratified for age and found higher failure rates for patients younger than age 40, compared with older individuals (48% vs 78%; P < 0.05). The long-term follow-up results of the same patient cohort showed similar results (16% vs 58%; P = 0.0014).[15] Another high-quality study

reported patients with clinical success being significantly older.[16] Moreover, a large prospective longitudinal cohort study found young age (<50 y) to be one of the strongest independent predictive factors for need of repeated treatment.[17] These findings were confirmed with data derived from the European Achalasia Trial, which also identified age as one of the predictive factors of need for re-dilatation in the pneumatic dilatation group.[5] Five-year follow-up results from the same cohort corroborated this finding. However, at the end of follow-up evaluation no significant difference in success rates was found between the surgery and dilatation groups.[18] In this trial, treatment outcome after laparoscopic Heller myotomy was not linked with age. Similar findings were made in 18 other studies reporting on surgical myotomy, of which 10 studies were classified as having low RoB, and 3 and 5 studies were rated as moderate and high overall RoB, respectively. However, 3 studies found favorable outcomes in surgically treated older patients (>40 y).[19–21] None of the studies on patients treated with POEM found any significant relation with age, and 3 randomized controlled trials on Botox also did not find any significant relation with age.[22–24] In 1 randomized controlled trial that compared 3 different Botox treatment regimens, non-responding patients tended to be younger, with a mean age of 49.3 ± 10 years compared with responders with a mean age of 57.5 ± 18 years (P = 0.03), however, in a multivariate adjusted model, age was no longer significant.[25]

Sex

Several high-quality studies reported on the association between sex and treatment response. The majority of included studies (90%; *n* = 43) did not find an association for any treatment. Three (1 low, 1 moderate, and 1 high RoB) of 23 studies on pneumatic dilatation, however, did find a link between sex and clinical outcome. In a multivariate analysis of patients treated with pneumatic dilatation, only male sex was found to be associated with poor outcome.[26] These results were replicated by 2 prospective studies that described an increased risk for younger men to fail pneumatic dilatation compared with older men.[3,10] As for patients treated with POEM, only 1 study found that male patients had significantly lower quality-of-life scores compared with females (odds ratio (OR), 1.90; 95% CI, 1.51–3.10; P = 0.042). With respect to laparoscopic myotomy, 1 single prospective study identified female sex as a predictor of superior postsurgical outcomes.[27]

Clinical Predictors

Symptoms

As can be seen in **Supplemental Table 6**, multiple studies reported on symptom severity (*n* = 21) and/or symptom duration (*n* = 26) as clinical predictors of treatment outcome. Only studies focusing on surgical or endoscopic myotomy found significant links (low RoB, *n* = 4; high RoB, *n* = 2). In patients treated with a Heller myotomy, high preoperative symptom scores were associated with increased clinical success.[27,28] Khajanchee *et al*[29] also found a significant association with symptom severity, but when correcting for confounders the clinical factor was no longer significant. One study in POEM patients found the opposite: an

Table 1. Cumulative level of evidence for explored prognostic factors

	PD			LHM	
	No association, *n*[a]/*N*[b] (%)	**Significant, *n*[a]/*N*[b] (%)**	**Level of evidence**	**No association, *n*[a]/*N*[b] (%)**	**Significant, *n*[a]/*N*[b] (%)**
Demographic factors					
Age	10/24 (42%)	14/24 (58%)	**Strong**	18/21 (86%)	3/21 (14%)
Sex	20/23 (87%)	3/23 (13%)	No predictor	19/20 (95%)	1/20 (5%)
Clinical factors					
Symptom severity	8/8 (100%)	0/8 (0%)	No predictor	4/7 (57%)	3/7 (43%)
Symptom duration	12/13 (92%)	1/13 (8%)	No predictor	9/10 (90%)	1/10 (10%)
Dysphagia	4/4 (100%)	0/4 (0%)	No predictor	3/3 (100%)	0/3 (0%)
Regurgitation	6/6 (100%)	0/6 (0%)	No predictor	4/4 (100%)	0/4 (0%)
Chest pain	6/9 (67%)	3/9 (33%)	**Inconclusive**	5/7 (71%)	2/7 (29%)
Pulmonary symptoms	1/2 (50%)	1/2 (50%)	Inconclusive[c]	0/0	0/0
Weight loss	6/6 (100%)	0/6 (0%)	No predictor	1/1 (100%)	0/1 (0%)
BMI	1/1 (100%)	0/1 (0%)	-	4/5 (80%)	1/5 (20%)
Prior treatment					
Prior treatment (NS)	1/1 (100%)	0/1 (0%)	-	1/3 (33%)	2/3 (67%)
Endoscopic treatment	0/0	0/0	-	5/6 (83%)	1/6 (17%)
Prior Botox	2/2 (100%)	0/2 (0%)	No predictor[c]	5/8 (63%)	3/8 (37%)
Prior PD	1/1 (100%)	0/1 (0%)	-	7/7 (100%)	0/7 (0%)
Prior LHM	0/2 (0%)	2/2 (100%)	Inconclusive[c]	2/4 (50%)	2/4 (50%)
Diagnostic factors					
Manometric subtype (CC)	2/4 (50%)	2/4 (50%)	**Strong**	2/7 (29%)	5/7% (71%)
LES (resting) pressure	16/18 (89%)	2/18 (11%)	No predictor	5/9 (56%)	4/9 (44%)
LES relaxation pressure	2/3 (67%)	1/3 (33%)	**Inconclusive**	6/6 (100%)	0/6 (0%)
Esophageal body pressure	8/9 (89%)	1/9 (11%)	No predictor	1/1 (100%)	0/1 (0%)
Barium height	4/5 (80%)	1/5 (20%)	No predictor	1/1(100%)	0/1 (0%)
Esophageal dilatation	9/11 (82%)	2/11 (18%)	No predictor	9/10 (90%)	1/10 (10%)
Mega/sigmoid esophagus	2/2 (100%)	0/2 (0%)	No predictor[c]	2/5 (40%)	3/5 (60%)
LES length	0/0	0/0	-	4/4 (100%)	0/4 (0%)
Gastric cardia diameter	3/3 (100%)	0/3 (0%)	No predictor	0/0	0/0

NOTE. Levels of evidence of (potential) predictors are shown in bold.

BMI, body mass index; CC, Chicago Classification; LES, lower esophageal sphincter; LHM, laparoscopic Heller myotomy; NS, not specified; PD, pneumatic dilatation; POEM, peroral endoscopic myotomy.

[a]Number of studies.

[b]Total number of studies.

[c]Evidence based solely on 2 studies.

	POEM			Botox		
Level of evidence	**No association, *n*[a]/*N*[b] (%)**	**Significant, *n*[a]/*N*[b] (%)**	**Level of evidence**	**No association, *n*[a]/*N*[b] (%)**	**Significant, *n*[a]/*N*[b] (%)**	**Level of evidence**
No predictor	7/7 (100%)	0/7 (0%)	No predictor	3/5(60%)	2/5 (40%)	**Inconclusive**
No predictor	5/6 (83%)	1/6 (17%)	No predictor	5/5 (100%)	0/5 (0%)	No predictor
Inconclusive	4/5 (80%)	1/5 (20%)	No predictor	2/2 (100%)	0/2 (0%)	No predictor
No predictor	1/2 (50%)	1/2 (50%)	Inconclusive[c]	5/5 (100%)	0/5 (0%)	No predictor
No predictor	0/0	0/0	-	0/0	0/0	-
No predictor	0/0	0/0	-	0/0	0/0	-
Inconclusive	0/0	0/0	-	0/0	0/0	-
-	0/0	0/0	-	0/0	0/0	-
-	0/0	0/0	-	1/1 (100%)	0/1 (0%)	-
No predictor	0/0	0/0	-	0/0	0/0	-
Moderate	6/7(86%)	1/7 (14%)	No predictor	2/2 (100%)	0/2 (0%)	No predictor[c]
No predictor	0/0	0/0	-	0/0	0/0	-
Inconclusive	1/1 (100%)	0/1 (0%)	-	0/0	0/0	-
No predictor	1/2 (50%)	1/2 (50%)	Inconclusive[c]	1/1 (100%)	0/1 (0%)	-
Moderate	1/3 (33%)	2/3 (67%)	**Moderate**	0/0	0/0	-
Strong	4/7 (57%)	3/7 (43%)	**Inconclusive**	0/0	0/0	-
Inconclusive	2/2 (100%)	0/2 (0%)	No predictor	3/3 (100%)	0/3 (0%)	No predictor
No predictor	1/1 (100%)	0/1 (0%)	-	1/1 (100%)	0/1 (0%)	-
-	0/0	0/0	-	1/1 (100%)	0/1 (0%)	-
-	0/0	0/0	-	1/1 (100%)	0/1 (0%)	-
No predictor	3/3 (100%)	0/3 (0%)	No predictor	2/2 (100%)	0/2 (0%)	No predictor[c]
Strong	0/1 (0%)	1/1 (100%)	-	0/0	0/0	-
No predictor	0/0	0/0	-	0/0	0/0	-
-	0/0	0/0	-	0/0	0/0	-

increased Eckardt score was the single independent factor associated with POEM failure 9.5 (range, 6–12) vs 7 (range, 2–12) (OR, 2.24; 95 CI, 1.39–3.93, P = 0.001).[30] Symptom duration also was investigated in the afore-mentioned study, but was not found to be significant. Liu *et al*[31] showed that POEM patients with a longer duration of symptoms (>10 y) had significantly higher failure rates compared with patients with a shorter duration of disease (hazard ratio (HR), 1.62; 95% CI, 1.04–2.52; P = 0.03).

All 18 studies that looked at a specific achalasia symptom found no associations for clinical outcome and dysphagia, reflux symptoms, or weight loss. Chest pain, however, seems to be an indicator of worse outcome after a Heller myotomy. According to 2 large prospective cohort studies, an increased chest pain score predicted a poor outcome (OR, 1.10; 95% CI, 1.04–1.16; P < 0.001)[32] and a score greater than 8 was indicative of clinical failure (OR, 3.476; 95% CI, 1.584–7.628; P = 0.0019).[33] Data from the European Achalasia Trial showed that pre-existing daily chest pain was a risk factor for treatment failure in general (HR, 2.8; 95% CI, 1.1–7.1; P = 0.03).[5,18] However, when looking at the treatment groups separately, authors were unable to confirm the predictive value of chest pain for treatment failure after a Heller myotomy. Chest pain predicted treatment failure and the need for re-dilatation only in patients who underwent pneumatic dilatation.

Prior treatment

Despite a large quantity of studies examining the relationship between prior treatment and clinical treatment response, evidence regarding the value of prior treatment as a predictive factor has been inconsistent and heterogeneous. Moreover, the evidence needs to be interpreted with the notion that these patients had symptom recurrence or the respective treatment previously failed. Few studies have investigated predictors for clinical response after endoscopic Botox injections and pneumatic dilation. One study stated that patients who previously failed dilation by means of bougie were at higher risk for failure on a second PD.[10] Another study found that the group of patients undergoing PD after a failed myotomy did less well than the untreated cases.[34] Of the 10 studies reporting on POEM, 3 studies (low RoB, *n* = 2) found an association with prior treatment.[31,35,36] An increased clinical failure rate was seen in patients previously treated compared with treatment-naive patients (hazard ratio, 2.16; 95% CI, 1.44–3.24; P < 0.001).[31]

Ngamruengphong *et al*[35] found that patients with a history of a Heller myotomy and pneumatic dilatation had a decreased clinical response to POEM (OR, 3.62; 95% CI, 1.26–10.39; P = 0.02; and OR, 2.93; 95% CI, 1.15–7.43; P = 0.02, respectively). However, only a prior Heller myotomy remained significant in multivariate analysis. Another POEM study found a similar association with prior surgery and clinical failure.[36] Prior treatment as a predictive factor was explored most often (*n* = 19) in patients treated with a laparoscopic Heller myotomy. Six studies, of which only 1 was rated as having a LoB, found differences in clinical success between treatment-

naive patients and patients who were treated earlier.[37–41] A history of prior PD does not seem to influence results because all studies investigating the link between prior PD and surgical outcome did not yield statistically significant results.[19,20,40,42–46] Prior Botox therapy, however, was identified as a predictor of surgical failure in 3 studies.[37,38,47] Only 1 study described an increased risk of surgical failure in patients previously treated with a Heller myotomy; prior LHM adversely affected clinical results.[45] No studies describing the effect of prior POEM on either treatment modality met our predefined inclusion criteria.

Surgical fitness

Six studies on Heller myotomy LHM and 1 PD study assessed body mass index as a predictor of outcome, but only 1 (low RoB) study showed that obese patients reported a worse outcome compared with patients with a normal body mass index (73% vs 91%). However, the investigators did not report the statistical level of significance of the difference.[48] The effect of American Society of Anesthesiologists Classification classification on treatment outcome was explored once, but no significant link was found.[43]

Diagnostic Predictors

Manometric subtype

Achalasia subtype has been linked to subsequent treatment response in several high-quality studies (rated as having a low risk of bias, *n* = 15). As for pneumatic dilatation, 4 of the 11 studies assessing achalasia subtype found an association with clinical success. Alderliesten *et al*[17] identified classic achalasia as a predicting factor for the need for repeated treatment during follow-up evaluation. Likewise, Pratap *et al*[49] found type II to be predictive of a good response. A post hoc analysis of the European Achalasia Trial showed that success rates in type II were high for both the LHM (93%) and the PD groups (100%).[8] Although not statistically significant, LHM had higher success rates than PD for patients with type III achalasia (86% vs 40%; P = 0.12).[8] Late follow-up results of the same trial confirmed that type III achalasia is indeed an important predictor of treatment failure, at least for PD.[18] Studies that specifically looked at surgical Heller myotomy also found type III to be predictive of poor treatment outcome.[32,50–52] Patients with type III achalasia had the highest incidence of failure (22.2% compared with type I and II, 3% and 3.4%, respectively; P = 0.01).52 With regard to POEM treatment, 3 of the 7 studies reported that achalasia type III was associated with failure.[53–55] Two Botox studies described that vigorous achalasia was found to be a predictor of good response.[25,56]

Other manometric factors

Pretreatment LES pressure was reviewed in several studies with contradictory findings. Five studies assessed resting baseline LES pressure and treatment outcome after Botox (*n* = 3) and POEM (*n* = 2), but found no significant relationship.[24,25,30,49,57] Most studies reported on patients treated with pneumatic dilatation (*n* = 18). Of these studies, 2 reported a significant,

but inconsistent, association; a resting LES pressure less than 30.5 mm Hg before treatment was indicative of treatment success in 1 study.[58] Conversely, Mehta *et al*[59] showed that responders tended to have higher LES pressures than non-responders (24% vs 80%; P < 0.001). However, both findings did not remain significant in a multivariate adjusted model and could not be replicated later by larger subgroup analyses in randomized controlled trials.[5,21,24] Studies on Heller myotomy that assessed LES pressure were more consistent; all 4 studies found that high preoperative LES pressure (>30 mm Hg) was an independent predictor of a good treatment response.[33,43,47,60] However, only 1 of these studies was rated as having a low risk of bias. LES relaxation nadir pressure was assessed less often. Of the 12 studies, only 1 study of patients treated with PD described that lower integrated relaxation pressure was a prognostic indicator of poor treatment outcome. Likewise, only 1 study found a positive association for esophageal body pressure and PD treatment outcome.[58]

Other diagnostic predictors

The presence of esophageal dilatation on barium swallow studies before treatment was studied in 24 studies as a predictor of treatment outcome, but most studies did not find a significant relationship (low RoB, *n* = 14; moderate RoB, *n* = 7). A dilated esophagus was linked with a negative outcome in patients treated with PD,[3,61] POEM,[31] and LHM.[33] In the latter study a sigmoid-shaped esophagus also was found to be of predictive value, as was found in 2 other surgical myotomy studies.[32,47] Interestingly, Moonen *et al*[18] found that a non-dilated esophagus was associated with failure. LES length, the presence of an endoscopic hiatal hernia, and gastric cardia diameter turned out not to be predictors of treatment outcome.[14–16,32,33,46,60,62]

Qualitative Synthesis of Patient-Specific Factors

As can be seen in **Table 1**, all predictors were categorized and classified based on consistency and corresponding level of evidence, using earlier-mentioned criteria. Factors assessed by 1 or 2 studies were by definition considered as a poor or inconsistent level of evidence, and therefore were omitted in this synthesis. When looking at the cumulative evidence for demographic factors, age was identified as a PD outcome predictor with a strong corresponding level of evidence, whereas sex turned out to be of no predictive value for any of the treatments. Of all clinical factors explored over the years, the majority proved not to be a predictor of treatment outcome. Symptom severity as a predictor of LHM outcome and the presence of chest pain for both LHM and PD outcome were identified as potential predictors with an inconclusive level of evidence. Prior treatment (not further specified) and prior Heller myotomy were classified as predictors of failure with a moderate level of evidence for treatment outcome after (redo) surgical myotomy. Likewise, prior LHM was a moderate predictor of repeat failure in POEM patients. Overall evidence for prior Botox was inconclusive but might potentially be of predictive value in patients treated with a Heller myotomy. As for diagnostic factors, both sigmoid-shaped esophagus (for LHM outcome) and manometric subtype, as classified according to the Chicago Classification, were identified as predictors of treatment outcome

after both PD and LHM with a strong level of overall evidence. Because of limited evidence, the predictive value of achalasia subtype was less pronounced for POEM and Botox therapy. Low pretreatment LES relaxation pressure might be an indicator of poor PD outcome, and, likewise, lower LES resting pressures might be predictive of poor treatment outcome after LHM. However, for both factors evidence was inconclusive. Remaining diagnostic factors, including esophageal dilation and barium height on barium swallow studies, did not predict treatment outcome.

Quantitative Synthesis of Patient-Specific Factors

Quantitative synthesis was planned for those predictors regarded as clinically relevant, with a strong level of cumulative evidence. Only studies that were compatible in terms of study type, outcome parameter, the statistical method used, and the prognostic effect measure described were eligible for statistical pooling. Five studies that reported on age and PD outcome were sufficiently compatible (total sample size, 562) for pooled analysis. Likewise, 5 LHM studies reporting on manometric subtype with a total of 1332 patients were sufficiently compatible and allowed statistical pooling. Data on other predictors with a strong level of underlying evidence (sigmoid-shaped esophagus, manometric subtype for POEM outcome) were unfit for pooled analysis owing to selective reporting, insufficient combined sample size, or a limited number of compatible studies. The data extraction tables for these studies and reasons for exclusion can be found in **Supplemental Table 7, 8 and 9**. A meta-analysis for age showed that patients with PD treatment success were significantly older (mean difference, 7.9 y; 95% CI, 1.5–14.3; I^2 = 76%) (**Figure 2**). Pooled analysis confirmed that manometric subtype III is associated significantly with treatment failure compared with type I (OR, 7.1; 95% CI, 4.1–12.4; I^2 = 0%) and type II (OR, 3.3; 95% CI, 2.0–5.5; I^2 = 0%) (**Figure 3**).

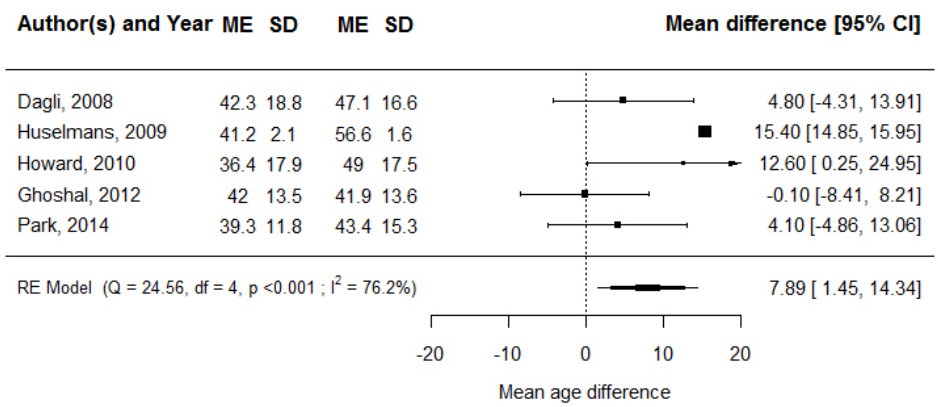
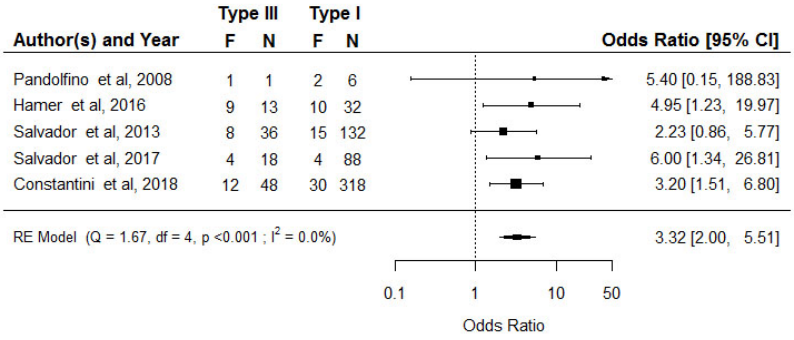


Figure 2. Meta-analysis of mean age difference. ME, mean age; RE, random effects



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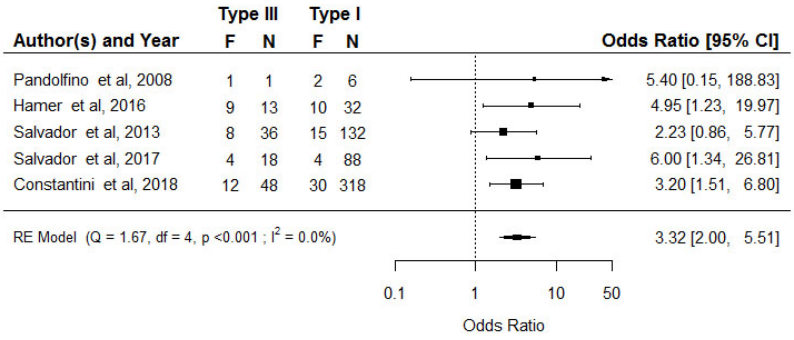

B

Figure 3. Meta-analysis of the relationship between laparoscopic Heller myotomy treatment outcome and manometric subtype. (A) Type III vs type I and (B) type III vs type II.
F, failure; *N*, patient number; RE, random effects.

DISCUSSION

Ideally, achalasia treatment improves esophageal emptying and remedies clinical symptoms for the remainder of the patient's life. However, this goal is not achieved in a substantial part of achalasia patients because no current treatment provides a definitive cure and overall efficacy deteriorates over time. Although the cause of treatment failure often is unclear, it is thought that esophageal hypersensitivity resulting from longstanding stasis is one of the factors contributing to refractory symptoms and incomplete clinical response.[63] At present, long-term treatment failure rates vary between 18% and 35%.[2,32,64] Not only is recurrence of achalasia symptoms burdensome and associated with a decreased quality of life,[65] treatment failure also may imply an increased risk of esophageal luminal distention in the long term.[66] Treatment optimization is of great importance because it may help to reduce risk of treatment failure and these long-term complications. Currently, therapeutic choices depend mainly on a center's expertise, patient preference, and individual comorbidities, but are not yet based on patient-specific demographic or clinical characteristics. A more personalized treatment plan could help optimize treatment outcome and reduce the risk of clinical failure.

Hence, predictive patient-specific and pretreatment factors would be valuable and could help guide patient-tailored treatment decisions. In this systematic review, we conducted a comprehensive search of 2356 citations, systematically assessed 117 citations, and identified and critically appraised all potential patient-specific predictors for clinical outcome in achalasia treatment. A key finding was that the overall evidence of most clinical factors explored over the years was rated as low, suggesting that these factors do not contribute to prognosis of treatment outcome. However, three patient-specific factors: age, manometric subtype, and the presence of a sigmoid-shaped esophagus, were classified as predictors with a strong level of cumulative evidence. A meta-analysis confirmed the predictive value of both age and manometric subtype in achalasia treatment outcome

In the early 1970s, Vantrappen *et al*[67] described that younger age may predict poor clinical outcome in patients treated with PD. This was confirmed by several later studies[14,15] and eventually in our meta-analysis. The reason for this remains unknown, although it has been suggested that the circular muscle fibers of the LES may be easier to disrupt with dilatation in the elderly.[25] Current evidence suggests that mega-esophagus or sigmoid-shaped esophagus is predictive of a less favorable outcome in patients treated with a Heller myotomy. Unfortunately, because of selective reporting and insufficient compatible data, the results of the LHM studies evaluating this predictor could not be pooled for quantitative assessment. Because there were few studies exploring the relationship between sigmoid-shaped esophagus and Botox, PD, and POEM, it remains unclear whether this effect can be attributed specifically to LHM, or advanced-stage disease is a predictor of clinical failure in general. Therefore, it would be imprudent to neglect a Heller myotomy in the treatment of advanced achalasia, especially because several studies have reported significant symptom relief after LHM in patients with sigmoid-shaped esophagus, with response rates of 54 to 100%.[68] For this reason, this predictive factor was not incorporated in our eventual clinical recommendation.

Since the introduction of high-resolution manometry and, concomitantly, the development of the Chicago Classification, it has been suggested that achalasia subtyping may be useful to determine choice of therapy. Multiple studies have reported different success rates for the 3 achalasia subtypes, with type I and particularly type III having an increased risk for treatment failure compared with type II.[69] Inferior response in type III patients often is attributed to spastic contractions in the esophageal body. Accordingly, our qualitative assessment showed that manometric subtype was one of the most clinically relevant predictors with a strong level of underlying evidence. Although only part of the studies was eligible for quantitative assessment, type III was found to be associated significantly with worse outcome in meta-analysis. Thus far, few studies have explored manometric subtype in the context of POEM and Botox treatment outcome, resulting in an inconclusive level of overall evidence. One of the key findings in a post hoc analysis of the European Achalasia trial was that achalasia patients with manometric pattern III had much higher success rates when treated with LHM than with

PD (86% vs 40%, respectively).[8] Previous studies in literature have described comparable success rates in this subset of patients.[9,49,51] These findings indicate that, in the treatment of type III achalasia, LHM should be preferred over PD. The therapeutic value of POEM in type III should be investigated further. Kumbhari *et al*[70] compared patients with type III achalasia who underwent POEM or LHM. Patients treated with POEM responded significantly better than patients treated with LHM (98.0% vs 80.8%). If more well-designed and adequately powered studies confirm these findings, it is likely that LHM and POEM will become the 2 therapies of choice for type III achalasia.

History of prior treatment, especially LHM, was found to be a predictor of treatment failure. In other words, previous treatment failure seems to be a risk factor for re-treatment failure. This finding most likely reflects a subset of patients with a more refractory type of achalasia that responds poorly to any treatment option. Although the total body of evidence still was rated as inconclusive, our results may indicate that previous Botox injections potentially compromise surgical outcome. It is thought that botulinum toxin injection induces local inflammation and eventually causes fibrosis, which may complicate Heller myotomy.[33,39–41]

In contrast to other specific symptoms that do not predict treatment outcome, preexisting chest pain does seem to be associated with treatment failure. Although studies on POEM and Botox therapy exploring this factor are scarce, our results seem to indicate that chest pain is a difficult symptom to resolve with any treatment. However, because chest pain is more common in patients with type III achalasia, one could speculate that this finding correlates with the presence of achalasia subtype III, rather than that it is an independent predictor itself, and vice versa.[51,63] Other identified potential predictors were symptom severity, pretreatment LES resting pressure, and LES relaxation pressure. Despite an abundance of studies examining the relationship between these factors and clinical treatment response, evidence remains inconclusive and these factors are not yet ready to be incorporated into clinical decision making. Interestingly, in contrast to common belief, the majority of included studies that evaluated sex (90%, *n* = 43) did not find an association for any treatment, suggesting that sex does not play a role in prognosis of treatment outcome

Current research has indicated that repetitive graded pneumatic dilatation, POEM, and laparoscopic Heller myotomy are comparable in terms of efficacy and safety rates.[1,4] Therefore, all 3 therapies are recommended as first-choice therapy in current clinical guidelines. Based on our systematic review and meta-analysis, both age and manometric subtype can be used in clinical decision making. Unfortunately, data on most potential predictors remains inconclusive or insufficient to produce other evidence-based recommendations. Therefore, based on our clinical experience, a critical appraisal of all observational and interventional achalasia studies assessing potential predictors, and the recommendations of current clinical guidelines, we propose an expert-opinion-based format to guide treatment decisions in achalasia (**Figure 4**).

Given short-term efficacy and a potentially increased risk of fibrosis after (multiple) injections, we suggest that Botox should be reserved for patients with severe comorbidities who are unfit for surgery, or for those who have good reason for temporizing a more definite treatment, such as pregnant patients and patients on temporary double-antiplatelet therapy.[37,38,47] PD, which is generally less invasive than POEM and LHM, also may be a reasonable alternative first option in high-risk patients with several comorbidities and/or advanced age. The more definite treatments of LHM and POEM will be more effective in adolescents, younger adults, and patients with type III achalasia, and should be recommended in patients with previous (endoscopic) treatment failure who are more likely to have a more refractory type of achalasia. Laparoscopic myotomy, which is a more invasive surgical procedure, might be less advisable in patients with previous extensive surgery, a history of peritonitis, or severe obesity. Because POEM is associated with a higher incidence of gastroesophageal reflux disease compared with PD and laparoscopic Heller, physicians should be more reluctant in advising POEM for patients with pre-existing gastroesophageal reflux disease, obesity, or those that are less willing to use life-long proton pump inhibitor therapy. In conclusion, patient-specific factors (seen in context with the efficacy and safety rates of the individual procedures, patient preference, and center expertise) should be taken into account when choosing a treatment strategy.

This review draws attention to the limited number of well-designed studies assessing multivariable predictors of achalasia treatment outcome and the lack of compatibility across

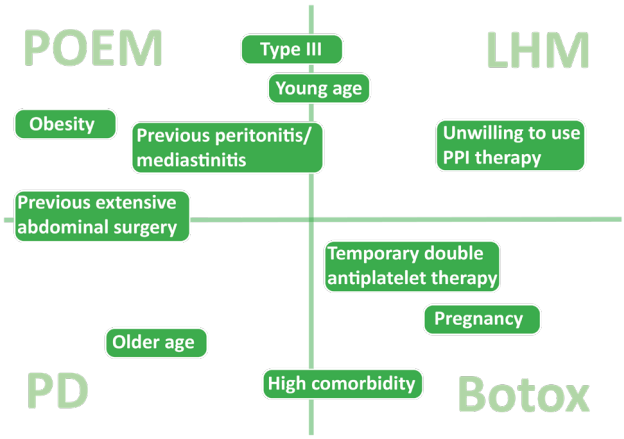

Figure 4. Proposed expert-opinion–based format to guide clinical decision making in achalasia management. Factors shown can be considered when selecting achalasia therapy. The quadrants represent the 4 therapeutic options. Patient-specific factors are placed within the quadrant of preferred therapy for that factor. Some factors are placed in 2 quadrants, indicating that both therapies are suitable.
LHM, laparoscopic Heller myotomy; PD, pneumatic dilatation; POEM, peroral endoscopic myotomy; PPI, proton pump inhibitor.

studies to allow statistical pooling. Qualitative synthesis of the existing data allows one to infer possible mechanisms or potential predictors, but there are a number of areas in which more research is required. First, the relationship between chest pain, manometric subtype, and treatment failure is poorly understood. Therefore, research should address the underlying mechanisms of chest pain and whether this interferes with poor outcome in type III patients. Second, future studies should focus further on the inconclusive or potential predictors to clarify their exact predictive role in treatment outcome. To do so, large, prospective, protocol-driven studies with unbiased and clear reporting of the methods and findings are warranted. More importantly, collaboration in terms of prospectively planned pooled analyses of (high-quality) studies and accessible individual patient data would contribute to high-quality evidence and would help realize evidence-based use of prognostic markers in clinical practice.

This review systematically assessed all available evidence on patient-specific predictors of treatment response. The findings of this review must be interpreted in the context of its limitations. First, outcome measures of the included studies were heterogeneous and often subject to investigator interpretation. Moreover, response was defined most commonly by clinical criteria, with only a minority of studies using the combination of clinical and manometric or radiographic end points. In line with this, because of high heterogeneity across primary studies, quantitative assessment was not feasible for the majority of candidate predictors. Moreover, the meta-analyses performed only included part of the studies because most data were not compatible enough to justify statistical pooling. Second, primary studies reported insufficient information to distinguish opioid-induced type III achalasia. This phenomenon was probably less well recognized in earlier studies. Third, most research on predictors has been performed in patients treated with pneumatic dilation or laparoscopic Heller myotomy. Therefore, future POEM studies are warranted to study the exact role of POEM and shed light on corresponding predictors of therapeutic response. In addition, the methodologic quality of studies differed greatly, but this was accounted for by using predefined criteria. Even with high heterogeneity among included studies, this review provides valuable information that provides more insight into individual patient factors and their possible role in guiding patient-tailored treatment strategies.

In conclusion, this systematic review used a methodologically rigorous strategy to identify and critically appraise all patient-specific predictors of treatment outcome in achalasia that have been explored over the years. Of all assessed factors, age and manometric subtype were identified as the strongest predictors of clinical response. Accordingly, we propose that treatment decisions should be tailored toward the individual patient by taking these characteristics into account, along with surgical risk, the expertise of the center, and the patient's preference. The majority of the factors explored, including sex, did not help in predicting achalasia treatment outcome.

AUTHOR CONTRIBUTIONS

L.P., A.B., and R.O.N. had a role in planning and/or conducting the study. R.O.N. F.v.E, and L.P. were involved in the acquisition of data. R.O.N., L.P., and A.B. had a role in collecting and/or interpreting data. R.O.N and A.B. had a role in drafting the manuscript. R.O.N and N.M. hade a role in conducting the meta-analysis. A.B. and A.S. had a role in reviewing and revising the manuscript for important intellectual content. All authors approved the final draft submitted.

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Search strategy

MEDLINE (PubMed)
(“Esophageal Achalasia”(Mesh) OR “Esophageal Motility Disorders”(Mesh) OR achalasia(tiab) OR esophageal motility disorder*(tiab) OR oesophageal motility disorder*(tiab) OR chicago classification(tiab))
AND
(“Dilatation”(Mesh) OR “Botulinum Toxins”(Mesh) OR dilatation*(tiab) OR dilation*(tiab) OR pneumodilatation*(tiab) OR pneumatic dilatat*(tiab) OR balloon(tiab) OR rigiflex(tiab) OR POEM(tiab) OR per oral endoscopic myotom*(tiab) OR peroral endoscopic myotom*(tiab) OR endoscopic myotomy(tiab) OR heller(tiab) OR heller myotomy(tiab) OR surgical myotomy(tiab) OR laparoscopic myotomy(tiab) OR minimally-invasive myotomy(tiab) OR cardiomyotomy(tiab) OR botox(tiab) OR botulin*(tiab) OR BoTx(tiab))
AND
(“Treatment Outcome”(Mesh) OR “Recurrence”(MeSH) OR “Postoperative Complications”(Majr:NoExp) OR “Mortality”(Mesh) OR outcome*(tiab) OR efficacy(tiab) OR failure*(tiab) OR success*(tiab) OR improv*(tiab) OR response(tiab) OR remission(tiab) OR relaps*(tiab) OR recurren*(tiab) OR recover*(tiab) OR re-intervention*(tiab) OR adverse event*(tiab) OR postoperative GERD(tiab) OR postoperative reflux(tiab) OR complication*(tiab) OR mortality(tiab) OR effect*(tiab) OR safe*(tiab) OR result(tiab))
NOT
(“Review” (Publication Type) OR “Case Reports” (Publication Type) OR case report*(tiab))
AND
english(Language)

Supplemental Table 1 continued

EMBASE (Ovid)	
1	esophagus achalasia/ or exp esophagus function disorder/ or (achalasia or esophageal motility disorder* or oesophageal motility disorder* or chicago classification).ti,ab,kw.
2	dilatation/ or botulinum toxin/ or (balloon or dilatation* or dilation* or pneumodilatation* or pneumatic dilatat* or rigiflex or POEM or per oral endoscopic myotom* or peroral endoscopic myotom* or endoscopic myotomy or heller or heller myotomy or surgical myotomy or laparoscopic myotomy or minimally-invasive myotomy or cardiomyotomy or botox or botulin* or BoTx).ti,ab,kw.
3	exp treatment outcome/ or recurrent disease/ or postoperative complication/ or exp mortality/ or (outcome* or efficacy or failure* or success* or improv* or response or remission or relaps* or recurren* or recover* or re-intervention* or adverse event* or postoperative GERD or postoperative reflux or complication* or mortality or effect* or safe* or result).ti,ab,kw.
4	1 and 2 and 3
5	"review"/ or case report/ or case report*.ti,ab,kw.
6	4 not 5
7	limit 6 to conference abstract status
8	6 not 7
9	limit 8 to english language
Cochrane Central Register of Controlled trials	
#1	Achalasia or esophageal motility disorder* or oesophageal motility disorder* or chicago classification:ti,ab,kw (Word variations have been searched)
#2	dilatation* or dilation* or pneumodilatation* or pneumatic dilatat* balloon or rigiflex or POEM or per oral endoscopic myotom* or peroral endoscopic myotom* or endoscopic myotomy or heller or heller myotomy or surgical myotomy or laparoscopic myotomy or minimally-invasive myotomy or cardiomyotomy or botox or botulin* or BoTx:ti,ab,kw (Word variations have been searched)
#3	outcome* or efficacy or failure* or success* or improv* or response or remission or relaps* or recurren* or recover* or re-intervention* or adverse event* or postoperative GERD or postoperative reflux or complication* or mortality or effect* or safe* or result:ti,ab,kw (Word variations have been searched)
#4	#1 and #2 and #3 in Trials

Supplemental Table 2. Selection criteria

Inclusion criteria	Exclusion criteria
- Human research subjects (>18 years of age) with achalasia - Primary, peer-reviewed studies - Studies that aimed to investigate prognostic factors for treatment outcome (clinical success/failure) for botox, PD, heller or POEM	- Editorials, letters, discussions, expert opinion papers, and systematic reviews of original research - Non-English abstracts - Studies older than 1990 - Retrospective studies < 50 patients - Prospective studies <30 patients - No clinical pre-treatment and patient-specific predictors described

Supplemental Table 3. Risk of bias (QUIPS) assessment of included studies (*n* = 75)

Supplemental Table 3 continued

Supplemental Table 3 continued

Green indicates low risk of bias, yellow indicates moderate risk of bias, red indicates high risk of bias.

To access the remaining supplemental tables accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at https://doi.org/10.1016/j. cgh.2019.10.008.

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Non-surgical treatment of esophageal perforation after pneumatic dilation for achalasia: a case series

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ABSTRACT

Esophageal perforation is the most serious complication of pneumatic dilation for achalasia and is traditionally managed by conservative therapy or surgical repair. We present four achalasia patients who underwent pneumatic dilatation, complicated by an esophageal perforation. All patients were treated successfully with endoscopic treatment: two patients with Eso-SPONGE® vacuum therapy, in the other two patients, esophageal defects were closed endoscopically using Endoclips. The time between dilatation and detection of the perforation was less than 24 h in all cases. Non-surgical treatment resulted in a relatively short hospital stay, ranging from 5 to 10 days, and an uneventful recovery in all patients. Based on our experience, endoscopic clipping and/or vacuum therapy are relatively new, valuable, minimally invasive techniques in the management of patients with small, well-defined esophageal tears with contained leakage and should be considered as primary therapeutic option for iatrogenic perforation in achalasia.

INTRODUCTION

Esophageal perforation is the most serious complication of pneumatic dilation for achalasia and is traditionally managed by conservative therapy or surgical repair.[1–3] With the introduction of new endoscopic techniques in the past decade, endoscopic management as primary therapy of iatrogenic perforation has been gaining ground.[4–7] We report four achalasia patients that underwent pneumatic dilatation complicated by an esophageal perforation. Two patients were treated successfully with Eso-SPONGE® vacuum treatment, in the other two patients the esophageal defects were closed endoscopically using endoclips. An overview of the clinical characteristics of the cases is displayed in **Table 1**.

Table 1. Clinical characteristics and course of treatment of esophageal perforation in four cases

	Case I	Case II	Case III	Case IV
Sex/age	F/39	F/55	F/70	F/80
BMI	22	21	20	32
Weight loss >10kg	+	+	+	-
Symptom duration (years)	<1	2	<1	10
Achalasia type	1	2	1	2
IRP-4 (mmHg)	22	37	24	¥
Barium Column height at 5 min (cm)	3.7	6.7	10.0	2.6
Esophageal width (cm)	3.0	3.2	1.5	4.3
Balloon size (mm)	40	40	40	35
Dilation pressure (PSI)	8	8	8	8
Site of perforation	Distal, L	Distal, V	Distal, L	Distal, R
Distance to EGJ (cm)	5	3	1	1
Length of perforation (cm)	3	3	5	4
Time until diagnosis (hours)	12	0	3	0
Extraluminal contrast on CT	Contained	Contained	No extraluminal contrast	Contained
Type of treatment	EsoSPONGE	EndoClips + esoSPONGE	EndoClips	EndoClips
Hospital stay (days)	10	7	5	6
Treatment success	+	+	+	+

EGJ: esophagogastric junction; I: Integrated relaxation pressure; L: left; R: right; V: ventral. After endoscopic closure with Endoclips. ¥Catheter did not pass the LES; therefore, IRP could not be calculated.

CASE PRESENTATION

Case I

A 39-year-old woman was referred to our department with symptoms of dysphagia. High-resolution manometry and barium esophagogram revealed achalasia type I. The patient was informed of the different treatment options and shared decision was made to perform pneumatic dilatation. Because of persistent symptoms after a 30 and 35-mm Rigiflex balloon dilation, she was re-dilated with a 40-mm balloon 4 weeks after the previous session. After an uneventful procedure, the patient was discharged, but after 12 hours she presented to the emergency room with symptoms of chest pain, vomiting and dyspnea. A CT scan of the chest was performed and showed a perforation of the distal esophagus with a paraesophageal fluid collection. The patient was kept nil per mouth and intravenous benzylpenicilline, gentamicin and metronidazole were started. An urgent upper endoscopy was performed and showed a 3-cm tear, located five centimeters above the diaphragm impression on the left lateral side. An overtube was introduced and placed proximal to the defect. Subsequently, the Eso-SPONGE® (B Braun Medical AG) was unfolded in the esophageal lumen. Since the chest CT scan revealed persistent mediastinal pneumatosis, the endosponge was retracted the next day, to make sure that it completely covered the perforation. The sponge was connected to a vacuum pump system with a negative pressure of 75mmHg and flushed three times daily. Parenteral nutrition was started. Over the course of the following days, the patient improved clinically and the sponge could be removed endoscopically after 7 days with a follow-up CT scan showing no more leakage. Endoscopic inspection showed a closed esophageal wall with the presence of some granulation tissue. The patient was discharged on a soft diet and proton pump inhibitor therapy and recovered quickly without further symptoms.

Case II

A 55-year old female patient previously diagnosed with achalasia type II for which she already had been dilated twice up to 35 mm, was admitted with an esophageal perforation after a 40-mm pneumatic dilatation. The perforation was detected after deflating the dilation balloon, revealing a 3-cm linear perforation just proximal to the Z-line (**Figure 1a**). An endoscope with cap was introduced and the perforation was closed with seven Endoclips (Olympus). The patient was kept nil per mouth and was started on the same antibiotic therapeutic protocol as case I. As the post-treatment chest CT scan showed extraluminal air and localized contrast spill in the mediastinal region, she was re-treated the next day by placement of the Eso-SPONGE® . Parenteral nutrition was started. Symptoms resolved soon after start of the vacuum therapy. Five days later, a CT scan confirmed absence of any esophageal leakage, and the sponge could be removed endoscopically after which a healed esophageal wall with granulation tissue became apparent (**Figure 1b,c**). The patient was discharged 2 days later. At 1-month follow-up, the patient reported improvement of dysphagia and was tolerating a normal diet without regurgitation or chest pain.

Case III

The third patient, a 70-year-old female with achalasia type I, was treated with a 40-mm diameter Rigiflex balloon because of lack of symptom relief after two previous (30 and 35 mm) dilatations. Four hours after the procedure, the patient developed severe chest pain whereupon endoscopic re-evaluation took place. A 5-cm long perforation became apparent (**Figure 2a**), which was closed with 15 endoclips (**Figure 2b,c**). An esophagogram and CT scan performed the next day did not show any esophageal leakage. The patient was started on intravenous antibiotics and a clear liquid diet along with duodenal tube feedings. The patients could be discharged 4 days later in good clinical condition.

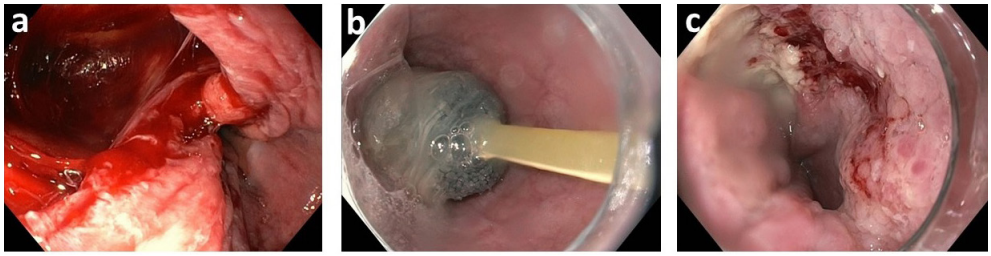

Figure 1. (a–c) Endoscopic view of the esophageal defect in case II. Immediately after pneumatic dilatation, a laceration 3 cm above the Z-line was observed (a). The patient was treated with Eso-SPONGE® vacuum therapy (b). After 5 days, endoscopic inspection showed healing of the esophageal wall defect with granulation tissue (c).

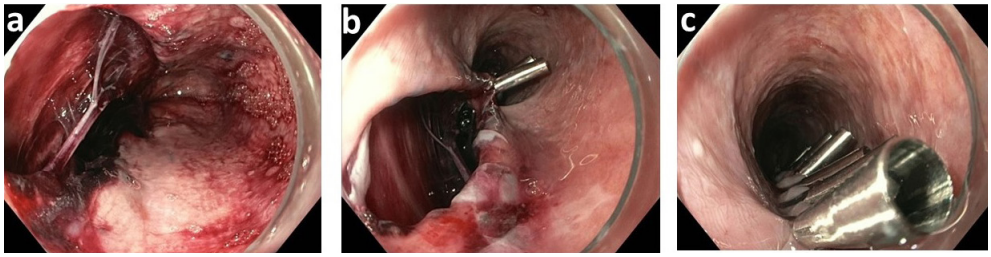

Figure 2. (a–c) Endoscopic images of esophageal perforation in case III. The defect was located just above the esophagogastric junction (a) and was successfully closed with 15 endoclips (b and c).

Case IV

An 80-year-old female was referred to our clinic because of long-standing dysphagia. The diagnosis of achalasia type II was established by barium esophagogram and manometry. Two weeks after a first 30-mm pneumatic dilation, the patient underwent a second dilation with a 35-mm diameter balloon. Endoscopic inspection immediately after dilation showed a 4-cm linear esophageal perforation just proximal to the gastroesophageal junction. The

perforation was closed endoscopically with eight endoclips. The patient was kept nil per mouth and tube-fed. The CT study performed the next day showed localized extraluminal contrast spill just proximal of the esophagogastric junction (**Figure 3**). Under intravenous antibiotics, symptoms resolved swiftly. A second chest CT scan 3 days later confirmed absence of extraluminal contrast and the patient was discharged 6 days post-procedure. After 12 weeks she visited our out-patient clinic and reported complete symptom remission.

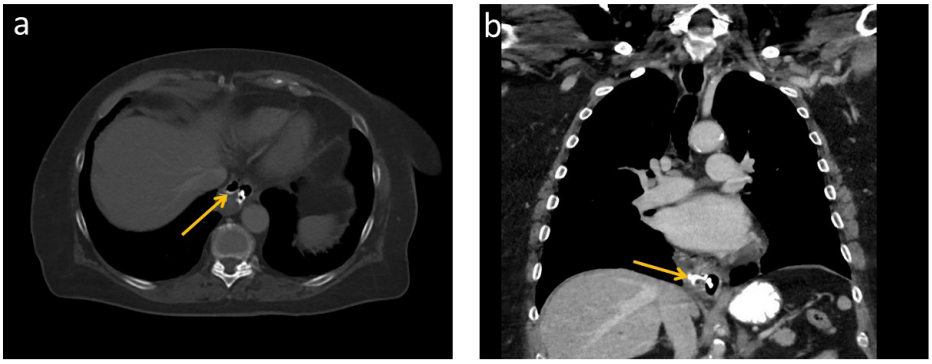

Figure 3. Axial (a) and coronal (b) CT scan of the chest showing evidence of contained esophageal perforation on the right side of the distal esophagus in case IV, including extraluminal air and contrast (arrows).

DISCUSSION

Although endoscopic pneumatic dilatation is regarded an effective and safe, nonsurgical therapeutic option for achalasia,[8,9] the procedure may be complicated by esophageal perforation. Typically, this occurs at the distal part of the esophagus, just above the level of the lower esophageal sphincter where the balloon is placed.[10] With an estimated occurrence of 0.5–5% of dilations in larger series, it is the most common and serious adverse event of balloon dilatation.[9,11] In this case series, we report four female patients who all suffered a perforation in a second or third dilation session. Other demographic, manometric or radiologic characteristics however, differed widely among our patients. Naturally, we cannot draw any conclusions in terms of predictive factors for esophageal perforation based on this case series. In literature, several risk factors have been suggested to increase the risk of perforation, including age, balloon size, a more stringent protocol with multiple graded dilatations, weight loss, long-standing symptoms, and higher dilation pressures.[12–16]

In patients with suspected esophageal perforation after pneumatic dilatation, a swift and decisive diagnostic approach is of utmost importance to limit diagnostic delay. Once the diagnosis is confirmed, nil per mouth, intravenous fluids, and broad-spectrum antibiotics should be initiated. Further management ranges from watchful waiting to surgical drainage or

even repair. Traditionally, most esophageal perforations were managed surgically.[1–3] Primarily in patients with larger tears and free mediastinal spill, surgical repair is still considered the strategy of choice. However, surgery involves considerable risks and therefore, previous studies have suggested that a less invasive treatment approach is more appropriate in clinically stable patients with contained perforation (e.g., well-defined tears with localized extraluminal spill).[16,17] In search of less-invasive methods to close esophageal perforations, endoscopic techniques, such as over the scope clips and esophageal stenting, have been explored over the past years. However, these techniques also come with additional risks, while results are not overwhelming.[4,6,7] Stents may dislocate in the dilated esophagus of the achalasia patient or may not close off the wall at the proximal end. Therefore, current guidelines mainly advice the use of endoclips in the endoscopic management of iatrogenic perforation.[5]

In our series, esophageal defects were closed successfully in all patients; in two patients the perforation healed and symptoms resolved after closure with endoclips; two other patients were effectively treated with the relatively new method of endoscopic vacuum therapy. Although both methods have previously been reported in patients with iatrogenic esophageal perforations,[18,19] this is the first series reporting these techniques in esophageal perforation caused by an endoscopic balloon dilatation in achalasia. One of the advantages of sponge vacuum therapy is the ability to clean the perforation cavity of debris using a minimally invasive technique. It enhances esophageal healing and formation of granulation tissue by reducing edema and bacterial contamination.[20,21] Of note, there are currently no comparative studies looking at the optimal endoscopic technique for iatrogenic perforations. The choice of endoscopic closure should depend on the duration of diagnostic delay, the size and location of the perforation and the endoscopic expertise available at the center. Clipping and/or vacuum therapy resulted in relatively short duration of hospitalization and an uneventful recovery in all our patients. In our center it is standard protocol to start patients on a liquid diet 3 days before the procedure. Hence, a clean esophagus without stasis and retention during the procedure might have contributed to treatment success in our series. Nonetheless, endoscopic therapy, combined with supportive treatment and careful observation, is a valuable option for treatment of patients with small (<5cm), well-defined esophageal tears with contained leakage and no signs of systemic infection. Based upon our experience, use of endoclips or sponge vacuum therapy should be considered in the treatment of iatrogenic perforation in achalasia. Prospective series and possibly comparative studies could assist to determine the definite role of these endoscopic techniques as non-surgical options of treating post-dilation perforations.

AUTHOR CONTRIBUTIONS

R.O.N. was involved in the acquisition of patient data. R.O.N, and A.B. had a role in collecting and/or interpreting data, and drafting the manuscript. A.B, B.T, P.F and J.B. had a role in reviewing and revising the manuscript for important intellectual content. All authors approved the final draft submitted.

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PART III

INABILITY TO BELCH SYNDROME

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The inability to belch syndrome: a study using concurrent high-resolution manometry and impedance monitoring

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ABSTRACT

Background

Although inability to belch has previously been linked to dysfunction of the upper esophageal sphincter (UES), its underlying pathogenesis remains unclear.

Aim

Our aim was to study mechanisms underlying inability to belch and the effect of UES botulinum toxin (botox) injections in these patients.

Methods

We prospectively enrolled consecutive patients with symptoms of inability to belch. Patients underwent stationary high-resolution impedance manometry (HRIM) with belch provocation and ambulatory 24-h pH-impedance monitoring before and 3 months after UES botox injection.

Results

Eight patients (four males, age 18–37 years) were included. Complete and normal UES relaxation occurred in response to deglutition in all patients. A median number of 33 (range 15–64) gastroesophageal gas reflux episodes were observed. Despite the subsequent increase in esophageal pressure (from −4.0 (−7.7–4.2) to 8 (3.3–16.1) mmHg; $P < 0.012$), none of the gastroesophageal gas reflux events resulted in UES relaxation. Periods of continuous high impedance levels, indicating air entrapment (median air presence time 10.5% (0–43)), were observed during 24-h impedance monitoring. UES botox reduced UES basal pressure (from 95.7 (41.2–154.0) to 29.2 (16.7–45.6) mmHg; $P < 0.02$) and restored belching capacity in all patients. As a result, esophageal air presence time decreased from 10.5% (0–43.4) to 0.7% (0.1–18.6; $P < 0.02$) and esophageal symptoms improved in all patients (VAS 6.0 (1.0–7.9) to 1.0 (0.0–2.5); $P < 0.012$).

Conclusions

The results of this study underpin the existence of a syndrome characterized by an inability to belch and support the hypothesis that ineffective UES relaxation, with subsequent esophageal air entrapment, may lead to esophageal symptoms.

INTRODUCTION

Belching or eructation is a physiological mechanism that enables venting of accumulated gaseous material from the stomach into the esophagus and pharynx. In healthy volunteers, intragastric air enters the esophagus via transient lower esophageal sphincter relaxations (TLESRs). The subsequent rapid increase in esophageal pressure to the level of the intragastric pressure, also known as common cavity phenomenon, causes distention of the esophageal body and stimulates stress receptors that will initiate upper esophageal sphincter (UES) relaxation and expulsion of air.[1,2]

In recent years, an increasing number of patients have been referred to our clinic because of an inability to belch, typically with symptoms of chest pain and audible gurgling noises from the chest. Although inability to belch as part of the gas-bloating syndrome occurs regularly post-fundoplication, an inability to belch from esophagus to oropharynx is rarely reported in medical literature, and its underlying etiology is virtually unknown. Three previous case reports described inability to belch and corresponding symptoms and attributed it to UES dysfunction.[3-5] A more recent study reported on 51 patients with inability to belch who were treated with injections of botulinum toxin (botox) into the cricopharyngeus muscle.[6] Interestingly, all patients reported ability to belch and relief of symptoms post-treatment, which may support the role of UES dysfunction in these patients.[6] Nonetheless, the question remains whether the symptoms are indeed the result of failure of the belch reflex pathway or are rather functional or behavioral in nature. Esophageal air transport patterns, UES physiology, and the effect of botox injections on UES function have never been objectively investigated in a series of consecutive patients.

Therefore, the aim of this study was to evaluate pathophysiological mechanisms underlying symptoms of inability to belch using concurrent high-resolution manometry and impedance monitoring with belch provocation and 24-h esophageal impedance monitoring. We aimed to assess the ability of the UES to relax in response to the influx of gas into the esophagus. Secondly, we aimed to study the effect of UES botox injections on pharyngoesophageal symptoms, UES pressure, and gas reflux patterns.

METHODS

Study subjects

For this cohort study, we included patients that presented with symptoms of inability to belch who were referred for treatment with UES Botox injections to the clinic of a Dutch teaching hospital between October 2019 and March 2021. Symptoms were defined as chest pain, gurgling noises and/or bloating at least three times a week, in combination with a self-reported inability to belch. Patients with a history of preexisting pharyngoesophageal disorders or surgery, or the use of medication affecting esophageal motility were excluded. The study

protocol was submitted to the local institutional review board. Formal evaluation was waived according to Dutch law (reference number W19_307#19.365). Written informed consent was obtained from all patients before study participation. The study was prospectively registered in the Dutch trial registry (NTR NL8494, trialregister.nl).

Study protocol

All patients were studied before and 3 months after UES botox injections. Each study day consisted of two parts and started with a stationary part using esophageal high-resolution impedance manometry (HRIM) to evaluate esophageal motility and UES and lower esophageal sphincter (LES) pressures in the supine position (**Supplemental Figure 1**). This was followed by a belch provocation test for which patients drank 500 mL of carbonated water (0 kcal, 7 g/L carbon dioxide gas). Using HRIM, gastroesophageal reflux of liquids and gas and UES function were recorded for the following 15 min in the upright position. Subsequently, patients went home with an ambulatory pH-impedance recording device. Gastroesophageal gas reflux patterns, air swallowing, and esophageal air presence time were monitored for 24 h. Gastric acid suppressants were discontinued 7 days before each study day. Pharyngoesophageal and abdominal symptoms and health-related quality of life were evaluated before and after treatment. A detailed description of the HRIM and ambulatory pH-impedance study protocol can be found in **Appendix A** in supplemental material.

Botulinum toxin injection in the upper esophageal sphincter

The botox injection procedures were carried out at the outpatient clinic during brief general anesthesia. The procedure was performed as described by Bastian et al.[6] In short, a laryngoscope was introduced to visualize the cricopharyngeus muscle. A 25-gauge butterfly needle was used with a laryngoscopy forceps. A total dose of 180 U of Dysport (equivalent to 50 U of Botox) in 1 mL was divided and injected over several locations of the sphincter. All procedures were performed by one and the same otorhinolaryngologist.

Data analysis

Key esophageal pressure topography metrics were calculated according to the Chicago classification V4.[7] For each gastroesophageal gas reflux event recorded during the 15-min recording HRIM period, intraluminal pressures immediately before and during the gas reflux event at the level of the UES and in the esophageal body were measured. Esophageal air presence time was defined as the percentage of time with continuous high impedance values ≥3000 Ω. A detailed description on data analysis methods and the used definitions can be found in **Appendix B** in supplemental material.

Statistical analysis

Throughout the manuscript, data are presented as median with range. Statistical analysis was performed using SPSS statistics (version 24; SPSS). Comparisons were analyzed using the

Wilcoxon signed rank test. Differences were considered statistically significant, when $P < 0.05$.

RESULTS

Patient characteristics and initial presentation

In total eight patients (four males, age 18–37 years) were included (**Table 1**). All patients described a long history of episodic gastroesophageal symptoms associated with gurgling noises in the chest and a self-reported inability to belch despite feeling the urge to do so during symptom episodes. Gurgling noises from the chest (100%), chest pain (75%), and bloating (100%) were the most commonly reported symptoms. Other symptoms included epigastric pain (53.5%), hiccups (37.5%), flatulence (37.5%), and nausea (37.5%). None of the patients reported symptoms of dysphagia or odynophagia. All patients described an inability to belch for as long as they could remember and reported avoidance of carbonated drinks and certain foods that would increase abdominal gas. Symptoms reportedly could be relieved by lying in the supine position. Occasionally, patients induced vomiting to vent air. Upper endoscopy and video laryngoscopy were performed in all patients. Besides incomplete glottal closure ($n = 1$) and a vocal cord polyp ($n = 1$), no major laryngopharyngeal abnormalities were found. A small endoscopic hiatal hernia was observed in three patients.

Table 1. Baseline characteristics of included patients ($n = 8$)

	n	(%)	Median (range)
Demography			
Male sex	4	50.0	
Age at inclusion (years)			27 (18–37)
BMI			24.9 (18.3–26.0)
Symptoms at presentation			
Gurgling noises from the chest	8	100.0	
Bloating	8	100.0	
Chest pain	6	75.0	
Epigastric pain	5	52.2	
Hiccups	3	37.5	
Flatulence	3	37.5	
Nausea	3	37.5	
Laryngoscopic findings			
Vocal cord polyp	1	12.5	
Incomplete glottal closure	1	12.5	
Endoscopic findings			
Sliding hiatal hernia	3	37.5	

BMI, body mass index; *n*, number of patients.

High-resolution impedance manometry

Esophageal motility was classified as ineffective (*n* = 5) or absent (*n* = 2) in the majority of patients with a median distal contractile integral (DCI) of 237 (17–754) mmHg·cm·s and a distal latency of 7.1 s (5.0–10.0). Complete and normal UES relaxation occurred in response to deglutition in all patients, with UES resting and residual relaxation pressures that fell within the normative range (95.7 (41.2–154.0) mmHg and −0.8 (−6.2–2.7) mmHg, respectively). Likewise, LES relaxation and resting pressures were normal (median integrated relaxation pressure (IRP) 7.2 (3.8–16.2) mmHg and basal LES pressure 20 (10.9–33.7) mmHg, respectively; **Table 2**).

Provocation (carbonated water drink) test

The basal UES pressure averaged 67.3 (53.5–101.5) mmHg during the 15-min recording period. After ingestion of the carbonated water, all patients began having spontaneous gastroesophageal gas reflux events and experienced typical gastroesophageal symptoms. A median number of 33 (15–64) gas reflux episodes up to the level of the lower border of the UES were observed. Despite the increase in esophageal pressure during these episodes, from −4.0 (−7.7–4.2) to 8 (3.3–16.1) mmHg ($P < 0.012$), none resulted in UES relaxation in any of these patients. The average UES pressure in response to arrival of the gas reflux event (115.2 (80.8–161.3) mmHg) was significantly higher than average basal UES pressure prior to the gas reflux event (67.3 (53.5–101.5) mmHg, $P < 0.012$). In other words; there was an increase in UES pressure instead of the expected UES relaxation. The gastroesophageal gas reflux episodes did elicit secondary peristalsis in 6 (75%) patients, with a median of 92.7% (78.3–100) of the gas reflux episodes being followed by secondary contractions. These contractions transported the esophageal air back to the stomach, which was observed as a return to baseline impedance level in antegrade direction. The typical sequence of events during a gastroesophageal gas reflux episode is presented in **Figure 1**. Striking were the periods of repetitive gas reflux where air seemed to oscillate up and down in the esophagus (**Figure 2**). In the two patients with a manometric diagnosis of absent contractility, there was also absence of secondary peristalsis in reaction to gastroesophageal gas reflux. These patients had longer periods of continually high impedance values during the 15-min recording period, complicating the recognition of the separate gas reflux episodes.

Ambulatory 24-h pH-impedance monitoring

During 24-h pH-impedance monitoring, patients reported a median of 9 (6–126) symptom episodes of inability to belch. The majority of these episodes (89.2% (66.7–100.0)) were associated with gastroesophageal gas reflux impedance patterns. During the ambulatory recording period, a median of 81 (7–185) gas reflux events occurred, but few air swallows (median 12 (4–41)) and supragastric belches (median 0 (0–1)) were observed (**Table 3**). In line with the repetitive gas reflux pattern observed on HRIM, similar periods of continuous high impedance levels, indicating air entrapment, were observed in 7 (87.5%) patients (**Figure 3**). The median 24-h esophageal air presence time was 10.5% (0.0–43.4). In one patient with

Table 2. High-resolution impedance manometry parameters before and after UES botox treatment

	Baseline		After treatment		
	Median	**range**	**Median**	**range**	**P value**
10 wet swallows (5 ml)					
Upper esophageal sphincter (UES) pressures					
Basal pressure (mmHg)	95.7	41.2–154.0	29.2	16.7–45.6	**0.017**
IRP (mmHg)	-0.8	−6.2–2.7	-5.9	−7.8–2.0	0.263
Lower esophageal sphincter (LES) pressures					
Basal pressure (mmHg)	20.0	10.9–33.7	20.5	11.2–41.9	0.866
Relaxation pressure (mmHg)	7.6	3.8–16.2	9.5	3.2–12.3	0.575
Esophageal motility parameters					
DCI (mmHg·s·cm)	237	17–754	390.5	22.0–948	0.050
DL (s)	7.1	5.0–10.0	6.7	5.0–9.0	**0.027**
Diagnosis according to Chicago classification					
Normal motility	1		1		
Ineffective esophageal motility	5		6		
Absent contractility	2		1		
15-min recording after provocation test					
Liquid reflux episodes	4	0–11	4	0–11	0.916
Gastroesophageal gas reflux episodes	33	15–64	12	3–36	**0.017**
% followed by secondary peristalsis	85.3	0–100	42.5	0–100.0	0.249
% followed by UES opening	0	0–0	30.0	5.0–100.0	**0.012**
Duration UES opening	NA	–	400	100–700	–
Averaged intraluminal pressures					
UES basal pressure preceding gas reflux event	67.3	53.5–101.5	35.6	12.3–45.1	**0.012**
UES pressure upon arrival of gas reflux event	115.2	80.8–161.3	38.3	18.3–108.5	**0.012**
UES nadir pressure during gas reflux event	63.4	51.0–89.2	13.5	9.2–38.2	**0.012**
Intra-esophageal pressure preceding gas reflux event	−4.0	−7.7 – 4.2	−3.8	−8.8–−0.9	0.310
Intra-esophageal pressure during gas reflux event	8.0	3.3–16.1	10.9	3.0–20.8	0.310

DCI, distal contractile integral; DL, distal latency; IRP, integrative relaxation pressure; LES, lower esophageal pressure; NA, not applicable; UES, upper esophageal sphincter.
For each gastroesophageal gas reflux episode, intraluminal pressures immediately before and during the gas reflux event at the level of the UES and in the esophageal body were recorded and averaged per patient.
Bold values denote statistical significance at the $P < 0.05$ level.

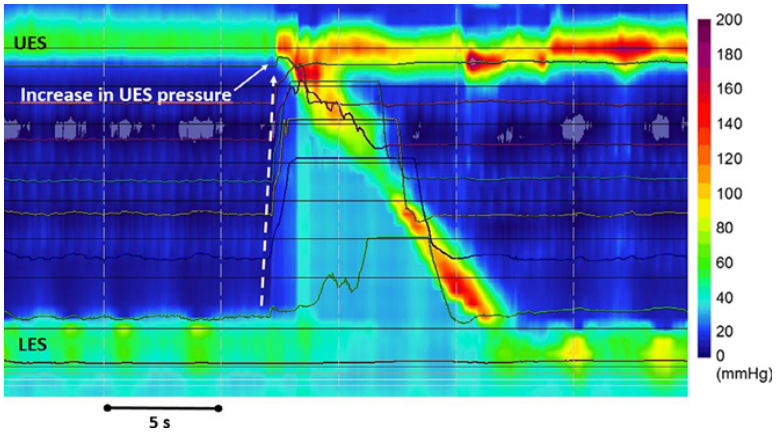

Figure 1. Gastroesophageal gas reflux event recorded with high-resolution impedance manometry in a patient with inability to belch. The sequence of events during a gas reflux event was characterized by: (1) retrograde flow of air from the stomach up to the level of the UES; (2) an increase in esophageal pressure to the level of the gastric pressure (common cavity phenomenon) (3) an increased or unchanged UES pressure; (4) failure of UES relaxation with consequently no venting of air across the UES (5) secondary peristalsis transporting the air from the esophagus back to the stomach

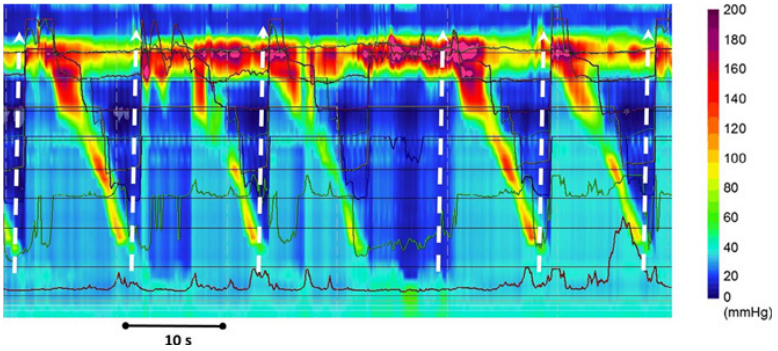

Figure 2. Repetitive gas reflux pattern recorded with high-resolution impedance manometry in a patient with inability to belch. Retrograde flow of gastric air (white arrows), in absence of subsequent UES relaxation, cleared from the esophageal body by secondary peristalsis and then immediately refluxed back into the esophageal body

Table 3. pH-Parameters before and after UES botox treatment

	Baseline		After treatment		
	Median	range	Median	range	P value
Symptom episodes of inability to belch*	9	6–126	0	0–15	**0.018**
Symptoms associated with gastroesophageal gas reflux (SI, %)	89.2	66.7–100.0	86.7	66.7–100.0	0.655
Acid exposure time (%)					
Total	2.2	0–20.2	3.4	0.4–15.0	0.779
Upright	1.6	0.1–9.0	4.7	0.4–10.9	0.161
Supine	1.9	0.0–48.4	0.5	0.0–25.6	0.327
Reflux episodes, *n*	17	2–48	40	3–128	0.092
Liquid	6	1–46	16	1–61	0.128
Mixed	6	1–17	14	2–67	0.068
Gas reflux episodes, *n*	81	7–185	57	13–130	0.624
Upright	81	6–185	50	13–129	0.674
Supine	1	0–9	1	0–13	0.917
Supragastric belches, *n*	0	0–1	0	0–24	0.109
Air swallows, *n*	12	4–41	21	13–42	0.161
Esophageal air presence time, %	10.5	0–43.4	0.7	0.1–18.6	**0.017**
Upright	17.3	0.0–54.0	1.2	0.1–27.8	**0.017**
Supine	0.0	0.0–1.3	0.0	0.0–0.0	0.180

n, number of patients; SI, symptom index.
*Esophageal symptoms specific for inability to belch (eg, gurgling noises from the chest or retrosternal pain) were taken into account.
Bold values denote statistical significance at the $p < 0.05$ level.

normal esophageal peristalsis, no esophageal air entrapment was observed. Both occurrences of gastroesophageal gas reflux episodes and air entrapment were rare in the supine position (1 (0–9) and 0 (0.0–1.3), respectively). The median acid exposure time was 2.2% (0.0–20.2) and the number of mixed and pure liquid reflux episodes fell within normal ranges 6 (1–17) and 6 (1–46), respectively. Two patients with severe ineffective or absent esophageal motility had a pathological acid exposure, primarily as a result of long periods of stasis in the night.

Effect of treatment

Symptom appraisal

All procedures were performed without complications. The majority of patients (*n* = 6) experienced swallowing difficulties the first 2 weeks post-treatment, which resolved spontaneously in all cases. Five patients reported to be able to belch spontaneously after

treatment with UES botox injections. Three patients still needed an extra maneuver to vent air, for example, contraction of the abdominal muscles to increase abdominal pressure or tilting of the head to the side. Seven patients (87.5%) were satisfied with the effect of botox therapy and described a complete or almost complete relief of symptoms. One patient had persistent symptoms of bloating and continued to experience mild symptoms of chest pain, while the sensation of gurgling noises had disappeared. Post-treatment VAS symptom scores for gurgling noises, bloating, retrosternal pain, epigastric pain, hiccups, and flatulence all improved significantly (all $P < 0.03$; **Supplemental Figure 2**). Quality of life (QoL) scores significantly improved post-treatment from 81% (69–85) to 91% (71–96; $P < 0.03$).

High-resolution impedance manometry and provocation test

High-resolution impedance manometry studies were repeated at 3-months follow-up. The calculated UES basal pressure during 10 wet swallows, and the averaged UES nadir pressure in response to gastroesophageal as reflux during the 15-min recording, showed a significant decrease compared to the baseline values (**Figure 4a,b**). Distal latency reduced from 7.1 (5–10) to 6.7 (5.0–9.0), $P < 0.03$. Treatment did not change LES resting and relaxation pressures (both $P > 0.05$), nor did it change DCI ($P = 0.05$) Before treatment, none of the gastroesophageal gas reflux events resulted in UES opening. At follow-up, 30 (5–100)% of the gas reflux episodes were followed by UES opening with a median duration of 400 ms (100–700). The number of gastroesophageal gas reflux episodes reduced from 33 (15–64) to 12 (3–36), $P < 0.02$; **Figure 4c**. In three patients, there was a large reduction in gastroesophageal gas reflux events; after a couple of initial belches in the beginning of the 15-min recording period, the gas was already expelled. In the remaining patients, there was reduction in gas reflux as well. However, the effect was less pronounced and UES opening occurred later. No difference was found between the proportion of the gastroesophageal gas reflux episodes that were followed by secondary peristalsis ($P = 0.249$).

pH-impedance monitoring

Post-therapy, esophageal air presence time had decreased significantly from 10.5% (0–43.4) to 0.7% (0.1–18.6; $P < 0.02$; **Figure 4d**). Likewise, the number of reported symptoms had significantly decreased after treatment (9 (6–126) vs 0 (0–15); $P < 0.02$). Treatment did not reduce the number of gastroesophageal gas reflux episodes (81 (7–185) vs. 57 (13–130); $P = 0.624$), nor did it change esophageal acid exposure times, the number of liquid and mixed reflux episodes, supragastric belches, and air swallows (all $P > 0.05$).

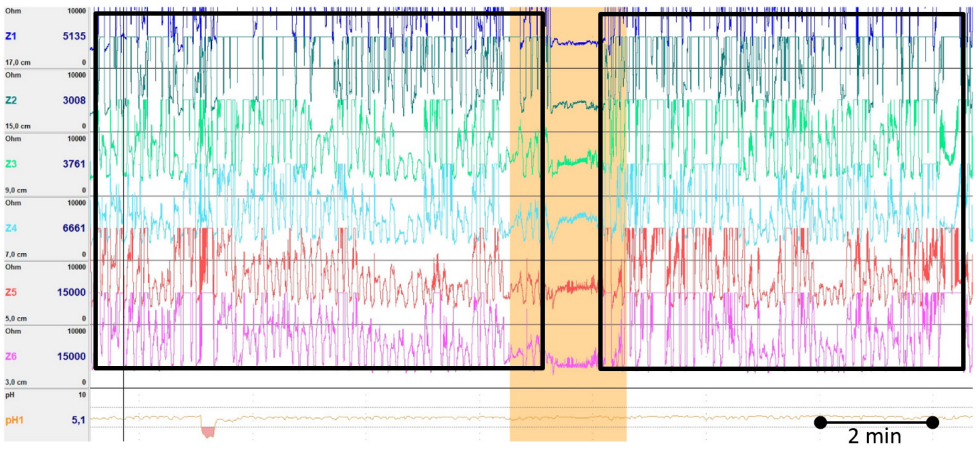

Figure 3. Esophageal air entrapment observed as periods (black rectangles) of continuous high impedance levels recorded with ambulatory pH-impedance monitoring in a patient with symptoms of inability to belch. The orange rectangular area represents the 2 min window the subject experienced a symptom

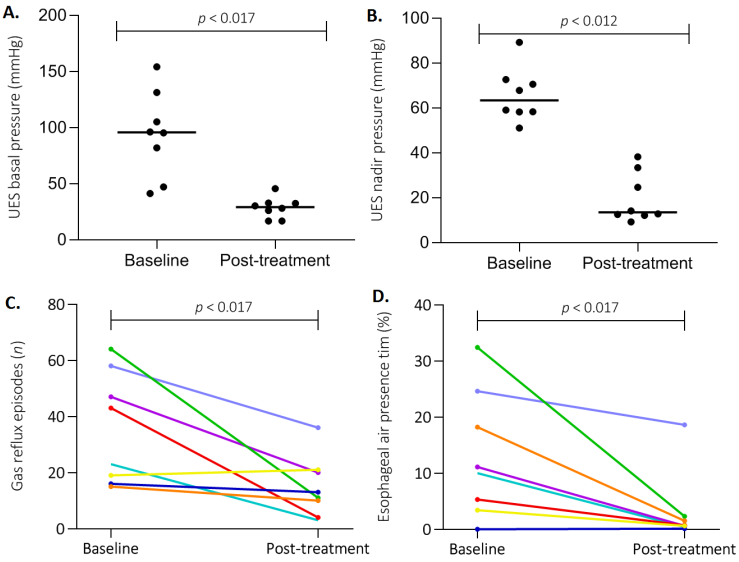

Figure 4. Upper esophageal sphincter basal pressure (a), average UES nadir pressure in reaction to gastroesophageal gas reflux (b), the total number of gastroesophageal gas reflux episodes observed during 15-min HRIM recording (c) and air presence time calculated during 24-h ambulatory pH-impedance monitoring (d) at baseline and post-treatment. After treatment, the UES basal and nadir pressure decreased significantly, facilitating UES opening and venting of air (P < 0.02). As a result, the number of gastroesophageal gas reflux episodes and air presence time reduced significantly (P < 0.02)

DISCUSSION

In the past few years, an increasing number of patients have been seeking medical attention because of a self-reported inability to belch in combination with esophageal or abdominal symptoms. This phenomenon, however, is barely described in literature, and underlying pathophysiological mechanisms are largely unknown. This is the first study that objectively assessed a group of these patients using combined HRM and impedance monitoring. Our findings provide evidence of the existence of a syndrome characterized by an inability to belch and support the hypothesis that ineffective UES relaxation in reaction to gastroesophageal gas reflux leads to esophageal air entrapment, which in turn causes esophageal symptoms. Patients were treated with UES botox injections, which reduced UES basal pressures and restored belching capacity in all patients. As a result, esophageal air presence time and esophageal symptoms improved in all patients at 3-month follow-up.

The typical clinical and manometric presentation of an inability to belch was previously described in case reports by Kahrilas *et al.* and by Waterman *et al.*[4,5] The patients described presented with similar repetitive gas reflux patterns and absence of UES relaxation, despite complete UES relaxation in response to deglutition, as was observed in our study subjects. In line with the previously reported findings, we found that the reflexogenic UES relaxation in response to an increase in esophageal pressure fails. It is noteworthy that the altered UES belch reflex in our patients was not simply an absent response but a paradoxical UES contraction. Contraction of the UES in combination with secondary peristalsis has been described as part of another UES reflex, usually activated by slow distention of the esophagus and thought to be important to prevent reflux of fluid boluses.[8] Surprisingly, seven out of eight patients in our cohort were diagnosed with ineffective or absent esophageal motility. Although this could be a coincidental finding, it is plausible that (severely) ineffective motility contributes to esophageal air entrapment, which more readily will lead to bothersome symptoms that will urge the patient to seek medical consultation.

In line with the high success rates for UES botox treatment reported by Bastian *et al.*, we observed a similar high efficacy in our subjects. As expected, botox therapy reduced the resting tone of the UES. Although three patients still needed additional maneuvers to force out air, all patients eventually showed manometrically UES relaxation in response to esophageal distention and were able to belch audibly. Several etiologies might underlie the UES dysrelaxation observed in these patients, including structural abnormalities, failure of neurophysiological mechanisms, or subconsciously learned behavior. Absence of any abnormalities found during upper endoscopy and video laryngoscopy rules out structural pathologies as an underlying cause. We found normal reflux of gas across the LES with rapid pressure increases in the proximal esophagus, suggesting that an effective stimulus was present. The observed normal UES resting and relaxation pressures in response to deglutition point toward failure of the belch reflex pathway on a neurophysiological level, rather than

to a problem of the UES opening muscles. During swallowing, the cricopharyngeal muscle relaxes and remains inactive while the UES lumen opens under the influence of distracting muscles, pharyngeal propulsion, and distention forces generated by bolus passage.[9,10] This suggests that pharyngeal contraction and bolus flow during deglutition could hypothetically compensate for an ineffective UES opening as a result of an impaired neuro-motor function. A previous physiological study confirmed that opening muscles are not active during belching.[11] Absence of these driving forces can mask UES dysrelaxation during swallowing. The observation that a muscle relaxant such as botulinum toxin enabled belching in all study patients supports the hypothesis that an alteration in neurophysiological function, either motor or sensory, underlies UES dysrelaxation, rather than an ineffective stimulus. Another important possibility for UES dysrelaxation in response to gastroesophageal gas reflux is a subconsciously learned behavioral response to avoid aspiration. This might explain why we see a paradoxical increase in UES pressure followed by secondary peristalsis in our subjects. The finding by Bastian *et al.*, that the therapeutic benefit of botox appears to last longer than its pharmacological effect, further supports this theory. Bastian *et al.* suggest that the temporally reduction in UES tone somehow retrains the patient to use the sphincter permanently in retrograde function. However, it must be stressed that further research is warranted before more definitive conclusions can be drawn regarding the pathogenesis of inability to belch. Moreover, the follow-up duration of our study was only 3 months, so the long-term efficacy of botox was not evaluated.

Inability to belch as underlying cause of gas-related symptoms is an unknown phenomenon and the vast majority of physicians is unaware of its existence. Currently, there are no guidelines or standardized diagnostic or therapeutic protocols for these patients. Although Bastian *et al.* suggest that the clinical syndrome can be diagnosed based upon symptoms alone, the list of potential causes that can give similar gastroesophageal complaints is long. Therefore, we recommend to first exclude important alternative diagnoses, before continuing with botox therapy. A diagnostic upper endoscopy and video laryngoscopy are helpful to rule out structural pathologies. Standard HRM is advised to assess esophageal motility. Impedance monitoring has a high sensitivity and reproducibility for the detection of air swallows and all types of reflux events, including gas reflux, and it is recommended to exclude alternative diagnoses such as aerophagia.[12,13] Additionally, we emphasize the importance of stimulating awareness among physicians to encourage better disease recognition, especially since there seems to be an effective therapy available that resolves symptoms in most patients.

Some limitations must be acknowledged. First, in absence of a control group, this study was not equipped to produce normative data on esophageal air presence time and UES pressures in response to gastroesophageal gas reflux, which would have been helpful to define normal values for diagnostic purposes. Second, it is important to realize that this study was conducted in a small cohort. Although the number of subjects was adequate to

generate convincing data on pathophysiological mechanisms associated with the inability to belch syndrome, further research is necessary to elucidate the exact cause of the defective belch reflex and to determine the true effect of botox therapy in these patients, preferably in a sham-controlled setting.

In conclusion, the findings of this study underpin the existence of a syndrome characterized by an inability to belch and suggest that a defective belch reflex underlies impaired UES relaxation. UES Botox therapy enabled belching in all patients and reduced esophageal air entrapment and esophageal symptoms.

AUTHOR CONTRIBUTIONS

RON, BK, JAS, LC, AB, and AS played a role in planning of the study. RON, JAS, JO, and AB had a role in conducting the study. RON and JO were involved in the acquisition of data. RON, BK, JMS, and AB had a role in collecting and/or interpreting data. RON played a role in drafting the manuscript. JAS, BK, DH, LC, JMS, AS, and AB played a role in reviewing and revising the manuscript for important intellectual content. All authors approved the final draft submitted.

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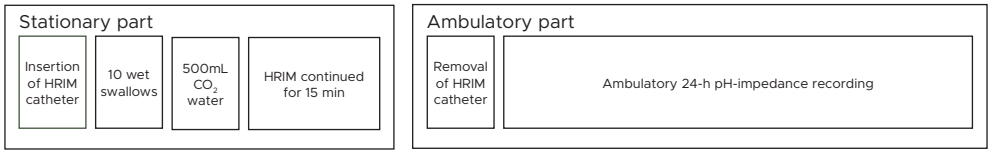
SUPPLEMENTAL MATERIAL



Supplemental Figure 1. Study protocol of stationary and ambulatory esophageal function testing

Appendix A. Study protocol HRIM and ambulatory pH-impedance monitoring

High-resolution impedance manometry

A combined high-resolution manometry and impedance (HRIM) catheter, 12 Fr in diameter, (Medtronic, Minnesota, USA), fitted with 36 solid-state pressure sensors at 1-cm intervals and 18 impedance measuring segments at 2-cm intervals was used. The catheter was introduced transnasally and positioned to measure from hypopharynx to stomach. All signals were sampled at a frequency of 100 Hz. Following a standardized protocol, patients were placed in supine position (20˚) and received 10 boluses of 5 mL water with an interval of 20s. Prior and subsequently to the wet swallows, a period of 30 s not swallowing was assessed for baseline measures. The catheter was retracted 10 cm and patients received 10 boluses of 10 and 20 mL water with an interval of 20 s, to assess UES pressures.[8] Thereafter, HRIM was continued for another 15 min in upright position, after ingestion of the carbonated drink, as described above.

Ambulatory 24-h pH-impedance monitoring

After the HRIM catheter was removed, a 24-hour pH-impedance study was carried out using a combined pH-impedance catheter assembly (Unisensor). The catheter contained six impedance recording segments which were located at 2–4, 4–6, 6–8, 8–10, 14–16 and 16–18 cm above the upper border of the manometrically localized LES and one antimony pH electrode which was placed 5 cm above the upper border of the LES. The impedance and pH signals were stored in a digital data logger (Ohmega, MMS, Enschede, the Netherlands), using a sampling frequency of 50 Hz and 1 Hz, respectively. Patients were instructed to press the event marker button on the pH data logger whenever they were experiencing symptoms. During the recording, the patients were instructed to consume 3 meals and 4 beverages at fixed times and to keep a diary in which they had to note symptoms, meal periods and the period spent in the supine position.

Appendix B. Data analysis

Stationary high-resolution impedance monitoring

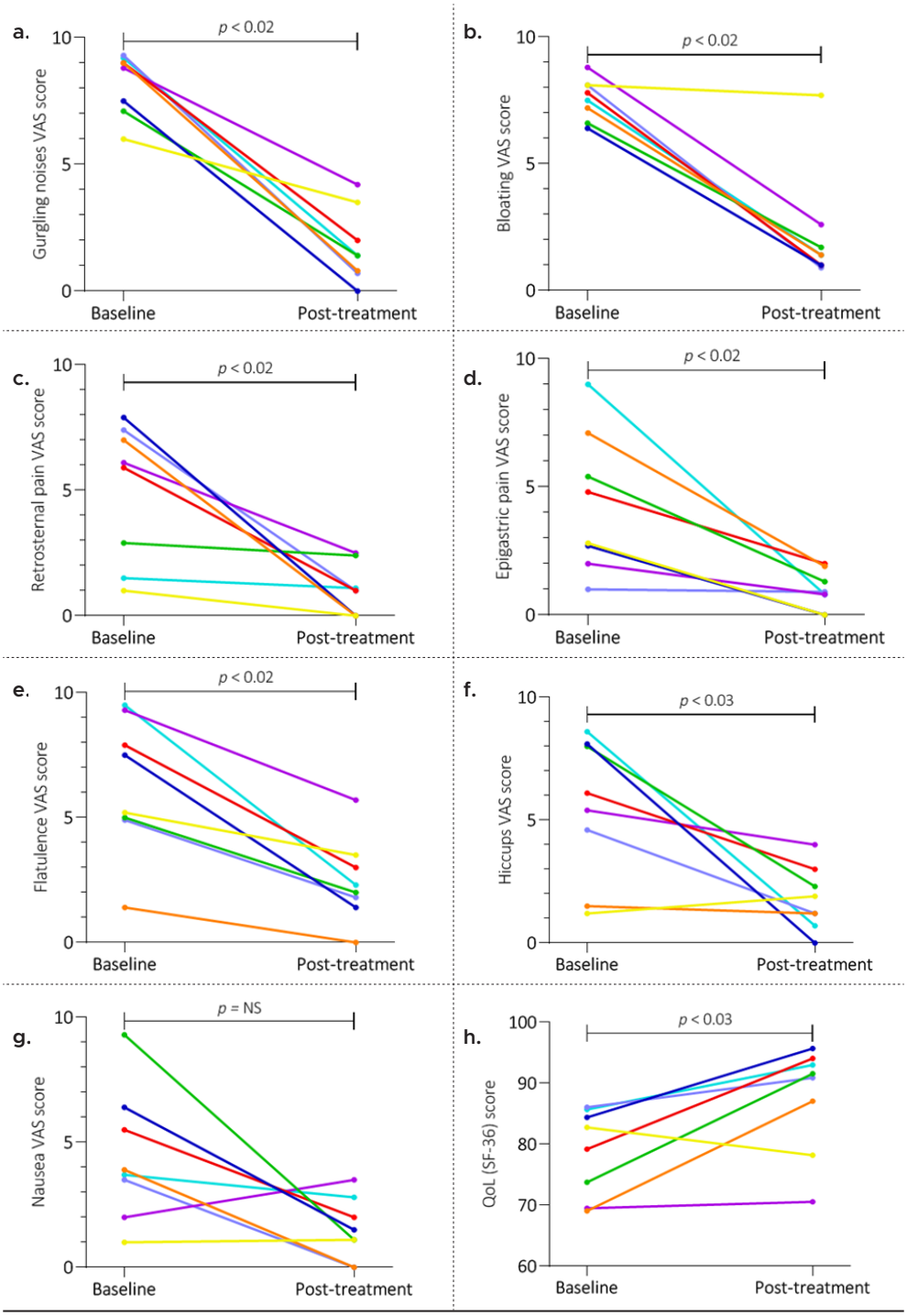
The HRIM studies were analyzed by dedicated software (Manoview), and evaluated according to the Chicago classification V4.[8] Key esophageal pressure topography metrics were calculated, including LES basal pressure, the 4s-integrated relaxation pressure (IRP), distal contractile integral (DCI), and distal latency (DL). Moreover, UES resting and residual pressures during wet swallows were determined. In the HRIM data that were recorded for 15 min after ingestion of the carbonated water, gas reflux and pressure events in stomach, LES, esophageal body and UES were analyzed as follows. Gastroesophageal gas reflux was defined as a rapid retrograde rise in impedance ≥3000 Ω in at least two consecutive channels reaching the most proximal impedance-recording segment.[9] For each gastroesophageal gas reflux episode, intraluminal pressures immediately before and during the gas reflux event at the level of the UES and in the esophageal body were measured. Moreover, UES pressure at the point where the gas reflux episode reached the lower UES border and nadir UES pressure were determined for every gastroesophageal gas reflux episode. The ability of the UES to open in reaction to intraesophageal air was scored if the UES nadir pressure in response to a gas reflux episode was equal to, or lower than, the intra-esophageal pressure during that gas reflux episode.[10]

Ambulatory 24-h pH-impedance monitoring

Ambulatory 24-hour pH-impedance tracings were analyzed manually. The first 2 hours and periods of meal consumption and beverages were excluded from the analysis. Gastroesophageal reflux events were detected using the impedance tracings and classified into liquid, mixed liquid-gas, and pure gas reflux episodes. Esophageal air presence time was defined as the percentage of time with continuous high impedance values ≥3000 Ω. Swallows were defined as a decrease in impedance moving from the most proximal recording segment in an aboral direction. Air swallows were defined as a swallow with an impedance increase of 1000 Ω or more in the most distal recording segment and a supragastric belch was defined as a rapid impedance increase (≥1000 Ω) moving in an aboral direction, followed by a return to baseline moving in the opposite direction within 1s.[9] Esophageal acid exposure time, defined as the percentage of time with pH <4, was assessed for the total 24-h period and for the upright and supine position. The correlation between symptoms and gas reflux patterns was analyzed using the symptom index (SI), with a positive correlation when symptoms were notified within 2 min from the start of the gas reflux pattern. The score was calculated as the number of specific esophageal symptoms associated with gastroesophageal gas reflux as a percentage of the total number of specific esophageal symptoms.

Clinical information and symptom questionnaires

All patients underwent a complete symptom assessment preceding the studies. Recorded data included duration and type of symptoms, demographics, medication use, intoxications, and medical history. Patients were asked to report VAS scores for the presence of symptoms including gurgling noises, chest pain, flatulence, the sensation of bloating, nausea, vomiting, hiccups and epigastric pain. The 36-Item Short-Form Health Survey (SF-36) was used to assess health-related quality of life.



Supplemental Figure 2. VAS scores for gurgling noises (a), bloating (b), chest pain (c), epigastric pain (d), flatulence (e), hiccups (f) and nausea (g), and quality of life (QoL) scores (H) before and after treatment.

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Summary

Discussion and future perspectives

SUMMARY

Esophageal peristalsis and the combined efforts of both esophageal sphincters ensure passage of foods, fluids and saliva into the stomach, while preventing backward flow of gastric contents. Failure of one of these elements may result in esophageal dysfunction. This thesis covers studies on three different esophageal motility disorders, namely, gastroesophageal reflux disease, achalasia, and the inability to belch syndrome.

Part I - Gastroesophageal reflux disease

The first part of this thesis consists of multiple studies on the added value of alternative diagnostic tools and therapeutics in the management of gastroesophageal reflux disease.

In **chapter 2** we describe a prospective study in which we assessed the diagnostic yield of routine esophageal biopsies in patients with refractory reflux symptoms. The prevalence of eosinophilic esophagitis (EoE) in this specific subgroup was low (4.7%). Presence of dysphagia, food bolus impaction, atopic background, and typical endoscopic features were the factors with the strongest association and diagnostic accuracy for EoE diagnosis. The diagnostic yield in patients lacking symptoms of dysphagia or endoscopic features was negligible (0% and 1.9%, respectively). Based on these findings, we concluded that esophageal biopsies should only be obtained in patients with refractory reflux symptoms who also present with dysphagia.

Although nighttime reflux symptoms are common, the presence of nocturnal reflux is seldom confirmed with a standard 24-hour pH study. In **chapter 3** we used prolonged (96-h) wireless pH monitoring to study the true prevalence and mechanisms of supine nighttime reflux. Prolonged pH monitoring provided objective evidence of reflux at night in the majority (67.4%) of patients who complain of nighttime reflux symptoms. Increasing the duration of a pH study from 24h to 72h or 96h, progressively improved the diagnostic yield and diagnostic accuracy for nocturnal reflux diagnosis. Reflux episodes with a lower nadir pH or longer acid clearance time were more prone to provoke nightly symptoms. These findings suggest that prolonged pH monitoring is preferred over a standard 24-h pH study in the assessment of patients with nocturnal reflux symptoms.

Chapter 4 describes a randomized placebo-controlled crossover trial studying the effect of STW5 (Iberogast®), a multi-target herbal preparation, on reflux symptoms in dyspeptic patients, specifically focusing on its potential underlying working mechanisms. Eighteen patients were assigned to four weeks of STW5 treatment followed by four weeks of placebo treatment, or assigned to the opposite treatment order. After 4 weeks of treatment with either placebo or STW5, esophageal sensitivity was studied with an esophageal acid perfusion test and patients underwent ambulatory 24-h pH-impedance monitoring. Although STW5 did

not significantly improve the total RDQ score, use of STW5 reduced GERD and regurgitation subscale symptom scores, which may suggest that STW5 is a potentially effective add-on therapy for reflux symptoms in dyspeptic patients. Nevertheless, the underlying working mechanisms through which STW5 acts, remain incompletely understood, as we found no statistical differences for acid perfusion sensitivity scores and esophageal motility after 4 weeks of STW5 treatment compared to placebo. However, the finding that patients with reflux esophagitis became less sensitive to acid after treatment with STW5 may point towards a reduction in esophageal hypersensitivity as a potential mechanism of STW5.

In **chapter 5** we retrospectively studied the natural course and long-term consequences of giant paraesophageal hernia in a large cohort of patients with a mean follow-up duration of 64 months. Of the 186 patients that were conservatively treated, a total hernia-related mortality of 1.6% was observed and a small subset of patients (1.1%) required emergency surgery. Hernia-related complications, varying from uncomplicated volvulus to strangulation, occurred in 8.1% of patients. The presence of obstructive symptoms such as vomiting, epigastric pain and chest pain were found to be associated with the occurrence of hernia-related complications during follow-up. As hernia-related death and morbidity were low in conservatively managed patients, we concluded that conservative therapy is an appropriate therapeutic strategy for asymptomatic patients with giant paraesophageal hernia.

Part II – Achalasia

The second part of this thesis comprises practical considerations and guidelines on the management of achalasia.

Because of the increasing body of evidence on achalasia and recent advances in its management, there was a growing demand for standardized treatment protocols. Therefore, we joined forces with other European physicians and scientists in the field of achalasia in an effort to provide an international and multidisciplinary evidence-based guideline. The result is the ESNM/UEG achalasia guidelines, provided in **chapter 6**. The 30 recommendations in these guidelines focus on achalasia diagnosis, treatment and follow-up and are based on a critical review of the best-available literature and the opinions of leading European achalasia experts.

Chapter 7 is a systematic review of the literature regarding potential patient-specific factors predictive for achalasia treatment outcome. We analyzed data from 75 studies (8 randomized controlled trials, 27 prospective cohort studies, and 40 retrospective studies) and a total of 34 different factors associated with treatment outcome were identified. Qualitative assessment showed age, manometric subtype, and presence of a sigmoid-shaped esophagus as factors associated with outcomes after achalasia treatment with a strong level of evidence. A meta-analysis confirmed that older age and manometric subtype 3 were associated with clinical response. In this study we provide an expert-opinion–based format to guide clinical decision

making in achalasia management with patient-specific factors that should be considered when selecting achalasia therapy.

Esophageal perforation is the most serious complication of pneumatic dilation for achalasia and is traditionally managed by conservative therapy or surgical repair. In **chapter 8** we presented four achalasia patients who underwent pneumatic dilatation, complicated by an esophageal perforation. All patients were treated successfully with endoscopic treatment: two patients with Eso-SPONGE® vacuum therapy, in the other two patients, esophageal defects were closed endoscopically using Endoclips. Non-surgical treatment resulted in a relatively short hospital stay, ranging from 5 to 10 days, and an uneventful recovery in all patients. Based on our experience, endoscopic clipping and/or vacuum therapy are new, minimally invasive techniques valuable in the management of patients with small, well-defined esophageal tears with contained leakage and should be considered as primary therapeutic option for iatrogenic perforation in achalasia.

Part III – Inability to belch syndrome

The final part of this thesis focused on the upper esophageal sphincter. We particularly studied the underlying pathophysiology of patients with an inability to belch.

Although an inability to belch as part of the gas-bloating syndrome regularly occurs after fundoplication, an inability to belch from esophagus to oropharynx is rarely reported in medical literature. It has previously been linked to dysfunction of the upper esophageal sphincter (UES). However, its underlying pathogenesis remains unclear. In **chapter 9** we aimed to study mechanisms underlying inability to belch and the effect of UES botulinum toxin (botox) injections in eight patients that were referred to our outpatient clinic with symptoms of inability to belch. All patients underwent stationary high-resolution impedance manometry (HRIM) with belch provocation and ambulatory 24-h pH-impedance monitoring before and 3 months after UES botox injections. Complete and normal UES relaxation occurred in response to deglutition in all patients. Moreover, we observed normal gastroesophageal gas reflux episodes in all study patients. However, none of these gas reflux events resulted in UES relaxation. During 24-h impedance monitoring, we observed esophageal air entrapment in all patients, indicated by periods of continuous high impedance levels. UES botox injections reduced UES basal pressure and restored belching capacity in all patients. As a result, esophageal air presence time decreased and esophageal symptoms improved in all study patients. The results of this study confirm the existence of a syndrome characterized by an inability to belch and support the hypothesis that ineffective UES relaxation, with subsequent esophageal air entrapment, may lead to esophageal symptoms.

DISCUSSION AND FUTURE PERSPECTIVES

Clinical care involving patients with esophageal dysfunction has changed significantly in the past decade under influence of new developments including high-resolution manometry, impedance planimetry, endoscopic treatment modalities such as per-oral endoscopic myotomy and studies providing new perspectives on diagnostic algorithms and therapeutics. Nevertheless, in the broad field of esophageal motility there is still much to be discovered. The studies described in this thesis address some of these knowledge gaps. We particularly focused on 1) the added value of alternative diagnostic tools and therapeutics in the management of gastroesophageal reflux disease, 2) practical considerations and guidelines in the management of achalasia, and 3) the underlying pathophysiology of the inability to belch syndrome.

Diagnostics in gastroesophageal reflux disease

Upper endoscopy and esophageal biopsy sampling

The diagnosis of gastroesophageal reflux is empirically made using a combination of the patient's clinical presentation, response to anti-secretory therapy, and objective testing with upper endoscopy and ambulatory pH monitoring.[1] The endoscope has long been the main tool to assess patients with symptoms suggestive of gastroesophageal reflux disease (GERD), primarily to exclude malignancies or other esophageal disorders that can give similar complaints, but also to assess the esophageal mucosa and the presence of erosive esophagitis, peptic strictures or Barrett's esophagus.[2] In case of erosive esophagitis, upper endoscopy is known to have a high specificity for the diagnosis of GERD.[3] The vast majority of patients with reflux symptoms however, lack any endoscopic abnormalities.[4] As a result, GERD diagnosis should not be made based on endoscopy alone, but endoscopy should be regarded a complementary diagnostic tool in the initial evaluation of patients with reflux symptoms. The exact role of esophageal biopsies as an adjunct to endoscopic evaluation is not so clear. Although it is evident that histology may sometimes provide useful diagnostic information, in particular to rule out other lesions, including candida esophagitis, eosinophilic esophagitis, intestinal dysplasia or metaplasia, exactly when esophageal biopsies should be taken remains a topic of discussion. The first reports on specific histologic hallmarks associated with GERD, date from the early '70s.[5] Despite attempts to develop histological grading systems with parameters such as papillae length, thickness of the basal cell layer, dilation of intercellular spaces, or presence of anti-inflammatory cells, it was found that histology correlated poorly with clinical and endoscopic findings.[6] Moreover, these histologic hallmarks are non-specific, as they reflect a general pattern of inflammation rather than a specific disorder. Thus, histologic characteristics may overlap with several other diseases of the esophagus, and therefore have a low diagnostic accuracy.[7] These limitations diminish the utility of histology in current clinical practice, although efforts are ongoing to identify new histologic parameters, for example on the localization of afferent nerves in the esophageal mucosa.[8] For this reason, routine esophageal biopsies are currently not recommended to diagnose GERD in patients with refractory reflux symptoms referred for upper endoscopy.

However, in the most recent version of the Rome criteria it is stated that esophageal biopsies should be obtained in all patients with refractory reflux symptoms, in order to rule out eosinophilic esophagitis (EoE).[9] In **chapter 2** we implemented this recommendation in clinical practice, and evaluated the diagnostic yield of routine esophageal biopsy sampling in patients with refractory reflux symptoms. We demonstrated that prevalence of EoE in this patient group was low. The diagnostic yield of biopsies in patients with reflux symptoms but without dysphagia or endoscopic features of EoE was even neglectable. The findings in this study strongly argue against routine esophageal biopsy sampling in all patients with refractory reflux symptoms. Presence of refractory reflux symptoms is one of the most prevalent reasons for referral to the gastroenterologist. Taking biopsies in all these patients will prolong endoscopic procedures and increase costs while the additional yield is limited. Rather, biopsies should be obtained only if patients exhibit specific clinical characteristics compatible with EoE, primarily dysphagia. This way no EoE cases are missed, while the number of abundant biopsies is minimized.

(Prolonged) pH-monitoring

The next diagnostic step in the evaluation of patients with refractory reflux symptoms is an ambulatory esophageal pH study, especially in those under consideration for anti-reflux surgery. Ambulatory pH-impedance monitoring is required to objectively document abnormal esophageal acid exposure or symptom association with reflux events. Standard catheter-based pH monitoring evaluates the pH in the distal esophagus, using a sensor positioned 5 cm proximal to the LES, often combined with intraluminal impedance, which monitors not only acidic reflux but also gas and non-acid liquids. In contrast to the traditional 24-hour catheter-based recording, the advancement of wireless monitoring has made it possible to record up to 96 hours. As a result of less patient discomfort and the extended monitoring period, wireless pH monitoring is associated with an increased sensitivity for detecting reflux events.[10, 11] An important group that may potentially benefit from prolonged recording are individuals with nocturnal reflux symptoms. Up to 80% of patients with GERD have nocturnal reflux symptoms, still these patients are poorly studied.[12, 13] In patients with nighttime reflux symptoms referred for ambulatory pH monitoring, the diagnosis of nocturnal reflux is seldom confirmed. It could be argued however, that a traditional 24-hour study with a catheter-based system is not the appropriate diagnostic tool to evaluate nocturnal reflux. It is known that nighttime reflux episodes occur infrequently and not every night, but are associated with an increased esophageal acid clearance time.[14, 15] Thus, a single nocturnal reflux episode could alter the clinical diagnosis of a 24-hour study and might lead to a sleep-deprived night, but is easily missed with pH monitoring limited to just one night. In **chapter 3** we studied this concept, and we found that just one or two nights with nocturnal reflux out of four nights, can cause bothersome nighttime symptoms in general, and that the majority of patients who complain of nighttime reflux symptoms had indeed reflux in one of the recorded nights. However, night-to-night variance was high and led to false-negative diagnoses when only

the first 24 hours were taken into account. Prolonged recording up to 48, 72 or 92 hours improved diagnostic yield and diagnostic accuracy for nocturnal reflux diagnosis. These findings underline that prolonged testing is a more appropriate diagnostic tool for the subgroup of patients with nocturnal reflux symptoms. Noteworthy, we found that reflux episodes with a lower nadir pH or longer acid clearance time were more prone to evoke nightly symptoms. This supports the hypothesis that despite the infrequent occurrence of nighttime reflux, one acidic reflux episode with long acid contact time can still cause bothersome nocturnal symptoms and a sleep-deprived night. By studying nocturnal reflux perception in the night, this study illuminated only a small aspect of the pathogenesis of nocturnal reflux. Despite its high prevalence, nocturnal reflux is still an underexposed topic in current literature and numerous questions remain unanswered.[16] Its pathophysiology and response to therapy undoubtedly differs from daytime reflux symptoms, and therefore this subgroup most likely will benefit from a different diagnostic and therapeutic approach. Future research should focus on underlying pathophysiological mechanisms and the role of sleep in nocturnal reflux, in order to improve diagnostic and therapeutic strategies in these patients.

Alternative therapeutics in gastroesophageal reflux disease

Pharmacological therapies

Proton-pump inhibitor (PPI) therapy forms the cornerstone of medical treatment of GERD, because of its high efficacy in both healing of mucosal damage and improvement of reflux symptoms.[17] Nonetheless, several studies have shown that use of standard-dose PPI results in either a partial or a complete lack of response in approximately 40% of patients with reflux symptoms.[18, 19] Treatment of these patients remains challenging because of the multifactorial pathogenesis underlying refractory reflux symptoms. A previous study evaluated GERD patients with and without persistent symptoms on PPI therapy.[20] Authors found that both esophageal hypersensitivity and the number of proximal reflux events, under the influence of transient lower esophageal sphincter relaxations (TLESRs), led to (partial) PPI failure. This suggests that further acid suppression has no benefit in the treatment of PPI-refractory reflux symptoms, but that researchers should redirect their focus towards therapies targeting TLESRs or esophageal hypersensitivity. With regard to TLESRs, numerous animal and clinical studies reported on potential pharmacological TLESR inhibitors such as GABA and mGluR5 receptor antagonists.[21] Although these reflux inhibitors reduce both the number of TLESRs and the number of reflux events, an unfavourable side-effect profile has prevented these reflux inhibitors from reaching market access. Unless future studies find a compound without significant side effects, the role of TLESRs inhibition as a valuable add-on to PPI therapy is limited to infrequent off-label use of the anti-spasmodic drug baclofen.

Visceral hypersensitivity is estimated to be present either by itself or overlapping with established GERD in as many as one-quarter of patients with persistent symptoms on PPI therapy,[22] and is therefore an alternative therapeutic target. Esophageal hypersensitivity can

be modulated by pharmacological agents directed at pain processing pathways in the central nervous system. Current options include tricyclic antidepressants and selective serotonin re-uptake inhibitors, however side effects are common, and often these do not outweigh the therapeutic benefits.[23] There is an increasing need for alternatives. A post-hoc analysis of a randomized controlled trial showed that STW5 (Iberogast®), an herbal preparation used in the treatment of functional dyspepsia, effectively reduced heartburn in dyspeptic patients.[24] As a previous animal study showed that STW5 decreased afferent sensitivity in rat small intestine, it is suggested that Iberogast might have an effect on esophageal visceral perception as well. Therefore, we studied the efficacy and working mechanisms of STW5 on reflux symptoms in dyspeptic patients in a randomized controlled setting (**chapter 4**). We did not find a significant effect in our primary outcome measure, but the RDQ subscales 'GERD' and 'regurgitation' were lower after 4 weeks of STW5 treatment compared to 4 weeks of placebo treatment. Although these findings may point towards a beneficial effect of STW5 on reflux symptoms, our findings will have to be confirmed in larger studies. Interestingly, subjects with reflux esophagitis became less sensitive to acid after treatment with STW5, thus one could hypothesize that reduction in esophageal hypersensitivity is a potential therapeutic target of STW5. Still, we were not able to clarify its exact working mechanisms, so future studies are awaited in which the efficacy and pharmacological mechanisms of STW5 and other comparable drugs are evaluated for the treatment of reflux symptoms.

New endoscopic options in reflux disease and hernia repair

Patients with persistent reflux symptoms under pharmacological therapy and a positive reflux-symptom association on ambulatory reflux monitoring can be considered for surgical anti-reflux therapies including laparoscopic fundoplication, or bariatric surgery in obese patients.[25] However, due to the invasive nature of a surgical fundoplication and associated risks, multiple attempts have been made to develop endoscopic procedures to restore the anti-reflux barrier, as an alternative to laparoscopic surgery. In the early 00s, multiple approaches were proposed, but either due to limited efficacy, severe adverse events, or requirement of costly devices, most of them were abandoned.[2] More recently, new techniques including trans-oral incisionless fundoplication and anti-reflux mucosectomy have been developed.[26, 27] Although the first clinical applications of the techniques in open label series show encouraging results, controlled data with long-term follow-up should be awaited before these endoscopic alternatives should become widely accepted as a standard treatment for reflux disease. Reasons for referral for anti-reflux surgery may include symptoms or esophagitis refractory to therapy, desire to discontinue pharmacological therapy, or presence of a large hiatus hernia.[2] Of note, the mere presence of an asymptomatic large sliding hernia is not an indication for surgical correction. For paraesophageal hernias however, there is an ongoing debate on the need of surgery, as these type of hernias can evolve in a gastric volvulus with risk of ischemia. Traditionally, elective surgery was often advocated for every patient, regardless of symptoms, with the objective of preventing acute complications and to avoid significant

mortality and morbidity associated with emergency surgery.[28, 29] However, more recent series suggest that the occurrence of life-threatening complications in untreated patients as well as the mortality rates for emergency surgery are much lower than initially estimated.[30-33] In the absence of reliable information on the natural course of disease, **chapter 5** aimed to provide long-term follow-up data of a substantial group of conservatively managed patients with a large paraesophageal hernia. We found a low hernia-related death rate and morbidity in these patients, leading to the conclusion that standard elective operation is not necessarily required in mild to moderately symptomatic patients. Elderly patients, who often bear extensive comorbidities, might benefit most from watch-full waiting. On the other hand, in younger patients deemed fit for surgery, elective hernia repair should not be disregarded in case of bothersome symptoms, especially because new advancements in laparoscopic or robot-assisted hernia repair have improved surgical outcomes tremendously in the past few years.[34] The decision to operate in the elective setting should depend on the nature and severity of a patient's symptoms as well as the patient's condition and age. We found that obstructive symptoms such as epigastric pain and vomiting were associated with the occurrence of complications at a later time. Therefore, we emphasize the importance of a patient-directed approach and consultation by a dedicated foregut surgeon, to weigh the risk–benefit profile of definitive repair versus observation, taking into account the extent and type of symptoms, hernia anatomy, the patient's age and perioperative risk.

Practical considerations and guidelines on achalasia management

The second part of this thesis focused on achalasia, an esophageal motility disorder for which the most far-reaching advancements have been achieved in the past decade. High-resolution manometry and the development of the international Chicago Classification have led to a major restructuring in the classification of esophageal motility disorders, in particular regarding the different achalasia phenotypes.[35] Other international and multidisciplinary collaborations have resulted in large, well-designed trials providing high-quality evidence.[36-38] Moreover, with the introduction of per-oral endoscopic myotomy (POEM), the therapeutic arsenal has expanded greatly. The rapid advancements in this field did also raise new clinical questions and shifted equipoise among physicians, which have urged the need for a clinical guideline on achalasia management. Along with a European team of gastroenterologists, radiologists, and gastrointestinal surgeons, we summarized four decades of achalasia research and formulated recommendations based on the best available evidence in a clinical guideline (**chapter 6**). Although this provides a framework that can assist clinicians in achalasia patient care, many knowledge gaps remain. One of the fundamental unanswered questions in achalasia research, is its pathophysiology. While the hypothesis that achalasia is caused by an infectious agent which triggers a neurodegenerative response in genetically susceptible individuals is widely accepted, the exact underlying pathogenesis remains unknown. Current therapies all aim to resolve symptoms by mechanical disruption of the LES, yet, in the ideal situation we would recognize early achalasia or even find a way to prevent or cure it. Research exploring gene

identification and inflammatory and neuronal pathways might be one of the means to achieve this ultimate goal in the future. One of the other big challenges in achalasia management are recurrent symptoms after therapy. Although a large body of evidence has shown that laparoscopic Heller myotomy, POEM, and repetitive graded pneumatic dilatation are all highly effective, a subset of patients will eventually require re-treatment.[36-38] Given the wide variety of potential causes of recurrent symptoms, it is of importance to undertake a thorough evaluation to select the appropriate therapy. This includes timed barium esophagram to assess esophageal emptying, endoscopy to exclude esophagitis or anatomic abnormalities, HRM to assess LES pressure and to exclude persistent spastic contractions in type III achalasia, and impedance planimetry might be a promising complementary tool to assess EGJ distensibility. Interestingly, there is no universal definition of what constitutes treatment failure. In most studies, a <50% improvement in symptoms or an Eckardt score of >3 is regarded as treatment failure, however, this does not include more objectively measured parameters such as esophageal emptying on timed barium esophagram. Symptom relapse after endoscopic and laparoscopic myotomy occurs in 10–20% of patients in the long term.[39-41] The best treatment approach depends on the etiology of symptoms, but in brief, pneumatic dilatation, (re-) POEM or (re-) surgery can all be considered. When gross anatomic abnormalities are present, surgery is preferred. If not, (re-) POEM or pneumatic dilatation can be effective. Both procedures show equally modest efficacy rates, with a presumed superiority for POEM over pneumatic dilatation.[39] On the other hand, pneumatic dilatation is often regarded a less invasive first step. Of note, due to small patient numbers, data on re-treatment is based on case series only. Therefore, prospective well-equipped trials, preferably in a randomized-controlled setting, are needed. One of the drawbacks of achalasia therapy, and another area warranting future research, is the occurrence of reflux after treatment. As a result of disrupting the anti-reflux barrier, the percentage of patients on PPI after achalasia therapy may be as high as 60%.[42, 43] Especially in patients treated with POEM, where no anti-reflux procedure is performed, the risk of post-treatment reflux is high. Choice of therapy should therefore take into account the risk of iatrogenic reflux disease and the willingness to use PPIs. New endoscopic anti-reflux treatments such as transoral incisionless fundoplication or anti-reflux mucosectomy may provide a future solution in this regard, however the limited body of evidence does not yet justify the use of these endoscopic techniques in clinical practice. Collaboration between endoscopists, surgeons and gastroenterologists will help to improve or develop new endoscopic anti-reflux treatments in the near future.

Towards patient-tailored therapy

One of the main topics of the past years is that achalasia therapy should be tailored to the individual patient. In **chapter 7** we explored potential patient-specific predictors and found that older patients (>45 years) responded better to treatment with pneumatic dilatation than younger individuals. Achalasia type III was associated with poor treatment outcome in general. Based on the results of our meta-analysis, paired with existing literature, a therapeutic

algorithm can be proposed. First, given the short-term efficacy and a potentially increased risk of fibrosis after (multiple) injections, botox therapy should be reserved for patients unfit for surgery or in whom a more definite treatment needs to be deferred, i.e. pregnant women or patients on temporary double platelet therapy. Pneumatic dilatation is a reasonable alternative in patients with comorbidities or at advanced age. The more definite treatments of endoscopic or surgical myotomy, will be more effective in younger patients and type III achalasia. One should be more reluctant with laparoscopic myotomy in patients with prior extensive abdominal surgery and suspected adhesions or severe obesity. Likewise, POEM is less advisable in patients with pre-existing GERD, obesity, or in those that are less willing to use life-long PPI therapy. In conclusion, a thorough clinical evaluation per patient is needed, where patient-specific factors, the risk–benefit profile of the different treatment options, the patient preference, and the expertise of the treatment team are weighted. In order to improve patient-tailored therapy, it is useful to further distinguish patient types that are likely to respond favourably to a certain therapy. The only way to achieve this, is by joining forces in terms of multicentric prospective acquisition of detailed patient data. This will enable us to produce high-quality evidence that would help realize evidence-based use of prognostic markers in clinical practice.

Pathophysiology of the inability to belch syndrome

for the third part of this thesis we move upwards to the upper esophageal sphincter (UES). In the past few years, an increasing number of patients have been seeking medical attention because of a self-reported inability to belch. Of note, it is important to make a distinction between an inability to belch as part of the gas-bloating syndrome which occurs regularly post-fundoplication, and the patients with an inability to belch from esophagus to oropharynx. The latter group is barely described in literature. Although the occasional case report has linked the phenomenon with UES dysfunction, esophageal air transport patterns and the role of UES function have never been objectively investigated in these patients and consequently, the pathogenesis remained virtually unknown.[44] In collaboration with the department of otorhinolaryngology, we studied and treated patients with symptoms of inability to belch (**chapter 9**). Using combined HRM and impedance monitoring with belch provocation we found that ineffective UES relaxation in response to gastroesophageal gas reflux leads to esophageal air entrapment in these patients. Moreover, botox injections in the UES reduced the resting tone of the UES and enabled belching in all patients. Our findings confirm the existence of a syndrome characterized by an inability to belch. One could question however, whether 'the inability to belch syndrome' is the correct term for this condition, as it must not be confused with an inability to belch due to ineffective opening of the LES, as part of the gas-bloating syndrome. Some previous studies have suggested 'retrograde cricopharyngeal dysfunction', however, it is not yet confirmed that the cricopharyngeal muscle is the sole problem in these patients. Even though this explorative pilot study was not designed to prove the exact location of the defect in the belch reflex pathway responsible for the abnormal

UES response, two main theories can be proposed. First, the finding that UES relaxation in reaction to deglutition was normal in all subjects, points towards an impaired UES neuromotor function rather than a problem of the UES opening muscles. It could be that pharyngeal contraction and bolus flow during deglutition compensate for an ineffective UES opening as a result of neurophysiological dysfunction. Another hypothesis is that subconsciously learned behavior to avoid aspiration causes an inability to belch. This might explain why we see a paradoxical increase in UES pressure followed by secondary peristalsis in our subjects. The finding that the therapeutic benefit of botox appears to last longer than its pharmacological effect, further supports this hypothesis. Nevertheless, the exact cause of the defective belch reflex remains incompletely understood. As botox therapy seems to benefit a large subset of patients, future studies are warranted to help increase our understanding of this disorder and the role of botox injection in its treatment, especially as it might be more prevalent than previously assumed.

Moving Forward

The studies described in this thesis have provided new insights in the pathophysiology, diagnostics and therapeutics of esophageal motility disorders. Nevertheless, many unresolved questions remain. One of the main topics for the future is patient tailored therapy. Not only concerning achalasia, but for the whole spectrum of esophageal motility disorders. Aided by new treatment options and a better understanding of the underlying pathophysiological mechanisms of the individual patient, tailored therapy will become increasingly possible, and will contribute to the improvement of patient outcomes across the globe. Previous international collaborations, leading to high-quality multicenter trials and multidisciplinary evidence-based classifications and guidelines, have shown us that joining forces can be the key in achieving this. Collaboration between clinical investigators and basic scientists, between disciplines, organizations and countries will help us to face the challenges that lie ahead and will enable us to move forward.

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Addendum

Nederlandse samenvatting
Contributing authors
List of publications
PhD portfolio
About the author
Dankwoord

NEDERLANDSE SAMENVATTING

Slokdarmperistaltiek en de gecombineerde inspanningen van beide slokdarmsfincters zorgen ervoor dat voedsel, vloeistoffen en speeksel de maag binnenkomen, terwijl het terugstromen van maaginhoud wordt voorkomen. Wanneer één van deze elementen niet goed functioneert, kan dit leiden tot oesofagiale dysfunctie. Dit proefschrift beschrijft onderzoek naar drie van dergelijke slokdarmmotiliteitsstoornissen, namelijk gastro-oesofageale refluxziekte, achalasie en het inability to belch syndroom.

Deel I - Gastro-oesofageale refluxziekte

Het eerste deel van dit proefschrift bestaat uit meerdere onderzoeken naar de toegevoegde waarde van alternatieve diagnostische hulpmiddelen en therapieën in de behandeling van gastro-oesofageale refluxziekte.

In **hoofdstuk 2** beschrijven we een prospectieve studie waarin we de diagnostische opbrengst van het routinematig afnemen van slokdarmbiopten bij patiënten met refractaire refluxsymptomen hebben onderzocht. De prevalentie van eosinofiele oesofagitis (EoE) in deze specifieke subgroep was laag (4,7%) en de diagnostische opbrengst daardoor zeer beperkt. Aanwezigheid van dysfagie, voedselimpactie, een atopische voorgeschiedenis en typische endoscopische kenmerken voor EoE waren de factoren met de sterkste associatie en diagnostische nauwkeurigheid voor een EoE diagnose. De diagnostische opbrengst van het routinematig afnemen van slokdarmbiopten bij patiënten zonder dysfagie of endoscopische kenmerken bleek verwaarloosbaar klein (respectievelijk 0% en 1,9%). Op basis van onze bevindingen concluderen we daarom dat alleen biopten genomen zouden moeten worden bij patiënten die naast refluxklachten ook klachten van dysfagie hebben.

Refluxklachten komen vaak ‘s nachts voor. De aanwezigheid van nachtelijke reflux wordt echter zelden bevestigd met een standaard 24-uurs pH-meting. In **hoofdstuk 3** hebben we verlengde (96-uurs) draadloze pH-metrie gebruikt om de werkelijke prevalentie en mechanismen van nachtelijke reflux te bestuderen. In de groep patiënten met nachtelijke refluxklachten, was er bij de meerderheid (67,4%) inderdaad sprake van nachtelijke reflux. Door de duur van een pH-onderzoek te verlengen van 24 uur naar 72 uur of zelfs 96 uur, vonden we een toegenomen diagnostische nauwkeurigheid en opbrengst voor de diagnose van nachtelijke reflux. Reflux-episoden met een lagere nadir pH of een langere klaringstijd waren geassocieerd met nachtelijke refluxklachten. Onze bevindingen suggereren dat verlengde (96-uurs) draadloze pH-metrie de voorkeur heeft boven een standaard 24-uurs pH-meting bij patiënten met nachtelijke refluxklachten.

Hoofdstuk 4 beschrijft een gerandomiseerde, placebo-gecontroleerde cross-over studie waarin we het effect van het kruidenpreparaat STW5 (Iberogast®) op refluxklachten bij dyspeptische patiënten hebben onderzocht. In het bijzonder hebben we gekeken naar

mogelijke onderliggende werkingsmechanismen van het middel. Negen van de in totaal achttien patiënten werden toegewezen aan vier weken STW5-behandeling gevolgd door vier weken placebobehandeling. De andere negen patiënten kregen de omgekeerde behandelvolgorde. Na 4 weken behandeling met placebo danwel STW5, werd de slokdarmgevoeligheid onderzocht met een slokdarmzuurperfusietest en ondergingen de patiënten een ambulante 24-uurs pH-impedantie meting. Hoewel STW5 de totale RDQ-score niet significant verbeterde, verminderden de regurgitatie en GERD symptoom subscores na het gebruik van STW5. Dit kan erop wijzen dat STW5 een potentieel effectieve aanvullende therapie is voor refluxklachten bij patiënten met dyspepsie. Het blijft echter onduidelijk wat de onderliggende werkingsmechanismen zijn van STW5. We vonden geen statistische verschillen voor de zuurperfusiegevoeligheidsscores en slokdarmmotiliteit na 4 weken STW5-behandeling in vergelijking met de placebobehandeling. De bevinding dat patiënten met reflux oesofagitis na behandeling met STW5 minder gevoelig werden voor zuur, zou er echter op kunnen wijzen dat een vermindering van slokdarmhypersensiviteit een mogelijk werkingsmechanisme is van STW5.

In **hoofdstuk 5** hebben we het natuurlijke beloop en de langetermijngevolgen van een grote para-oesofageale hernia (of intrathoracale maag) bestudeerd in een groot cohort van patiënten met een gemiddelde follow-upduur van 64 maanden. Van de 186 patiënten die conservatief werden behandeld, werd een totale hernia-gerelateerde mortaliteit van 1,6% waargenomen. Een kleine subgroep (1,1%) had een spoedoperatie nodig. Hernia-gerelateerde complicaties, variërend van ongecompliceerde volvulus tot strangulatie, kwamen voor bij 8,1% van de patiënten. De aanwezigheid van obstructieve symptomen zoals braken, epigastrische pijn en pijn op de borst bleken geassocieerd te zijn met het optreden van hernia-gerelateerde complicaties tijdens follow-up. Omdat de hernia-gerelateerde sterfte en morbiditeit laag waren bij de conservatief behandelde patiënten, concludeerden we dat conservatieve behandeling een geschikte therapeutische strategie is voor patiënten met een asymptomatische intrathoracale maag.

Deel II – Achalasie

Het tweede deel van dit proefschrift omvat praktische overwegingen en richtlijnen voor de behandeling van achalasie.

Vanwege de toenemende hoeveelheid literatuur over achalasie en de recente ontwikkelingen in achalasie behandeling, is er een toegenomen vraag naar gestandaardiseerde behandelprotocollen. In samenwerking met andere Europese artsen en wetenschappers op het gebied van achalasie hebben we een internationale en multidisciplinaire evidence-based richtlijn ontwikkeld. Het resultaat hiervan is de ESNM/UEG achalasie richtlijn, weergegeven in **hoofdstuk 6**. Op basis van de expert-opinion van vooraanstaande Europese achalasie onderzoekers en een kritische review van beschikbare literatuur bevat deze klinische richtlijn 30

aanbevelingen, gericht op de diagnostiek, behandeling en follow-up van achalasie patiënten.

Hoofdstuk 7 betreft een systematisch literatuuronderzoek naar mogelijke patiënt-specifieke factoren die voorspellend kunnen zijn voor de uitkomst van een achalasiebehandeling. We analyseerden gegevens van 75 studies (8 gerandomiseerde trials, 27 prospectieve cohortonderzoeken en 40 retrospectieve studies) en vonden in totaal 34 verschillende factoren welke mogelijk geassocieerd zijn met behandeluitkomsten. Kwalitatieve beoordeling van de data toonde dat leeftijd, manometrisch subtype en aanwezigheid van een sigmoïd-vormige slokdarm de factoren waren met een sterke associatie met de uitkomst na achalasiebehandeling. Een meta-analyse bevestigde dat hogere leeftijd en manometrisch subtype 3 geassocieerd waren met klinische respons. Op basis van onze bevindingen bieden we in deze studie een handig format dat kan helpen bij de klinische besluitvorming voor achalasie behandeling.

Slokdarmperforatie is de meest serieuze complicatie van pneumodilatatie in de behandeling van achalasie, en wordt traditioneel conservatief, dan wel chirurgisch behandeld. In **hoofdstuk 8** presenteren we vier achalasiepatiënten waarbij de behandeling met pneumodilatatie gecompliceerd werd door een slokdarmperforatie. Alle vier patiënten werden succesvol behandeld met een endoscopische behandeling. Twee patiënten werden behandeld met Eso-SPONGE® vacuümtherapie, bij de andere twee patiënten werden de slokdarmdefecten endoscopisch gesloten met Endoclips. Deze niet-chirurgische behandelingen resulteerden in een relatief korte ziekenhuisopname, variërend van 5 tot 10 dagen, en een voorspoedig herstel bij alle patiënten. Op basis van onze ervaringen, zijn endoscopisch clippen en/of vacuümtherapie waardevolle nieuwe technieken in de behandeling van patiënten met kleine slokdarmperforaties. We adviseren om ze als een eerste therapeutische optie te beschouwen voor iatrogene perforaties bij achalasie patiënten.

Deel III - Inability to belch syndrome

Het laatste deel van dit proefschrift is gericht op de bovenste slokdarmsfincter. We hebben de onderliggende pathofysiologie bestudeerd van patiënten met een onvermogen tot boeren.

Hoewel een onvermogen tot boeren regelmatig optreedt na een fundoplicatie als onderdeel van het gas-bloating syndroom, is er in de literatuur weinig bekend over een onvermogen tot boeren van slokdarm naar orofarynx. Eerder is dit in verband gebracht met dysfunctie van de bovenste slokdarmsfincter, echter de onderliggende pathogenese blijft onduidelijk. In **hoofdstuk 9** hebben we mogelijke mechanismen bestudeerd die ten grondslag kunnen liggen aan het niet kunnen boeren. Daarnaast hebben we gekeken naar het effect van botox injecties in de bovenste slokdarmsfincter bij acht patiënten met deze klachten. Alle patiënten ondergingen een gecombineerde high-resolution impedantie manometrie en een ambulante 24-uurs pH-impedantiemeting voorafgaand aan en 3 maanden na botoxbehandeling. Vóór de botox injecties leidde geen enkele gastro-oesofageale gasreflux episode (boer) tot

relaxatie van de bovenste slokdarmsfincter, terwijl er wel sprake was van een volledige en normale relaxatie van de bovenste slokdarmsfincter gedurende het slikken. Opvallend waren de lange perioden van continue hoge impedantiewaarden tijdens de pH-impedantie meting, passend bij aanwezigheid van veel lucht in de slokdarm. De botoxbehandeling verminderde de basale druk van de bovenste slokdarmsfincter en herstelde het vermogen om te boeren in alle patiënten. Als gevolg hiervan nam de hoeveelheid lucht in de slokdarm af en namen de typische slokdarmklachten in alle patiënten af. De resultaten van deze studie bevestigen het bestaan van een syndroom dat wordt gekenmerkt door een onvermogen tot boeren en ondersteunen de hypothese dat ineffectieve UES-relaxatie, met daardoor ophoping van lucht in de slokdarm, kan leiden tot slokdarmklachten.

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LIST OF PUBLICATIONS

This thesis:

Utility of Routine Esophageal Biopsies in Patients With Refractory Reflux Symptoms.
R.A.B. Oude Nijhuis, W.L. Curvers, M. van der Ende, T.V.K. Herregods, J.M. Schuitenmaker, A.J.P.M. Smout, A.J. Bredenoord.
Am J Gastroenterol. 2021 Apr;116(4):816-820.

Characterisation of patients with supine nighttime reflux: observations made with prolonged wireless oesophageal pH monitoring.
R.A.B. Oude Nijhuis, R. Sweis, H. Abdul-Razakq, J.M. Schuitenmaker, T. Wong, R.I. Rusu , J.M. Oors, A.J.P.M. Smout, A.J. Bredenoord.
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The effect of STW5 (Iberogast) on reflux symptoms in dyspeptic patients: a double-blind randomized placebo-controlled crossover trial
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Submitted.

The natural course of giant paraesophageal hernia and long-term outcomes following conservative management.
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European guidelines on achalasia: United European Gastroenterology and European Society of Neurogastroenterology and Motility recommendations.
R.A.B. Oude Nijhuis, G. Zaninotto, S. Roman, G.E. Boeckxstaens, P. Fockens, M.W. Langendam, A.A. Plumb, A.J.P.M. Smout, E.M. Targarona, A.S. Trukhmanov, B.L.A.M. Weusten, A.J. Bredenoord.
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Scand J Gastroenterol. 2020 Oct;55(10):1248-1252.

The inability to belch syndrome: a study using concurrent high-resolution manometry and impedance monitoring
R.A.B. Oude Nijhuis, J.A. Snelleman, J.M. Oors, B.F. Kessing, D.A. Heuveling, J.M. Schuitenmaker, L. ten Cate, A.J.P.M. Smout, A.J. Bredenoord.
Neurogastroenterol Motil. 2021, in press.

Other publications:

The natural course of eosinophilic esophagitis and long-term consequences of undiagnosed disease in a large cohort.
M.J. Warners, **R.A.B. Oude Nijhuis**, L.R.H. de Wijkerslooth, A.J.P.M. Smout, A.J. Bredenoord.
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Investigator initiated research in times of COVID-19: Let's go digital!
J.M. Schuitenmaker, **R.A.B. Oude Nijhuis**, A.L. Bredenoord, P. Fockens, A.J. Bredenoord.
Neurogastroenterol Motil. 2020 Nov;32(11):e14011.

Normative reference values for esophageal high-resolution manometry in healthy adults: A systematic review.
L.G. Alcala-Gonzalez, **R.A.B. Oude Nijhuis**, A.J.P.M. Smout, A.J. Bredenoord.
Neurogastroenterol Motil. 2021 Jan;33(1):e13954.

Letter: is wireless oesophageal pH monitoring the best technique to evaluate night-time reflux? Authors' reply.
J.M. Schuitenmaker, **R.A.B. Oude Nijhuis**, A.J. Bredenoord.
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Associations between sleep position and nocturnal gastroesophageal reflux: a study using concurrent monitoring of sleep position and esophageal pH and impedance.
J.M. Schuitenmaker, M. van Dijk, **R.A.B. Oude Nijhuis**, A.J.P.M. Smout, A.J. Bredenoord.
Accepted for publication in Am J Gastroenterol.

Sleep positional therapy for nocturnal gastroesopageal reflux: a double-blind, randomized sham-controlled trial.
J.M. Schuitenmaker, T. Kuipers, **R.A.B. Oude Nijhuis**, M.P. Schijven, A.J.P.M. Smout, P. Fockens, A.J. Bredenoord
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PHD PORTFOLIO

Name PhD student:	Renske Oude Nijhuis
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Supervisor:	Prof. dr. A.J. Bredenoord & Prof. dr. A.J.P.M. Smout
Co-supervisor:	-

	Year	Workload (ECTS*)
PhD training		
General courses (graduate school)		
Basic course legislation & organization of clinical research (BROK)	2018	1.0
Practical Biostatistics	2018	1.1
Advanced Topics in Biostatistics	2019	2.1
Clinical Epidemiology: Causality & Confounding	2018	0.9
Systematic review	2018	0.6
Project management	2018	0.6
Seminars, workshops and master classes		
Bi-weekly seminars in gastroenterology	2017 - 2021	1.5
Weekly clinical motility meeting	2017 - 2021	3.0
Gut club	2017 - 2021	1.0
GRADE master class	2018	0.7
Cambridge proficiency exam	2019	3.0
Oral presentations		
United European Gastroenterology week (2)	2020	1.0
FNM Meeting	2018	0.5
NVGE voorjaarscongres (3)	2018, 2020	1.5
AG&M PhD-retreat (2)	2018, 2019	1.0
Poster presentations		
Digestive Disease Week (1)	2018	0.5
United European Gastroenterology week (2)	2020	1.0

*ECTS: European Credit Transfer System

PhD Portfolio continued

	Year	Workload (ECTS*)
PhD training		
Attended (inter)national conferences		
Digestive Disease Week (2)	2018, 2019	1.0
United European Gastroenterology week (2)	2018, 2020	1.0
Amsterdam Live Endoscopy (3)	2018, 2019, 2020	1.5
NVGE Voorjaarscongres (3)	2018, 2019, 2020	1.5
Teaching		
Lecturing		
Achalasia UEG guideline webinar	2020	0.5
Medtronic training days (4)	2020 – 2021	1.5
Tutoring		
Margot van der Hoek, master thesis	2020	1.0
Leah Prins, extracurricular	2019	0.5
Parameters of esteem		
Grants		
UEG guideline grant	2019	
Awards and prizes		
NVGE best student award	2018	
Abstract selected for best of DDW	2021	
Other		
AG&M PhD retreat organizing committee	2019	

ABOUT THE AUTHOR

Renske Oude Nijhuis was born in Oldenzaal on the 3rd of December, 1991. She grew up with her younger brother Jerre in the small but cosy town of Fleringen in the east of the Netherlands. After attending atheneum at the St. Canisius college in Almelo, she took the train north to study medicine at the Rijksuniversiteit Groningen as from 2010. During her studies, she joined medical sorority Usus Cognitus, fulfilled the role of board member for ISCOMS (International Student Congress of (bio)Medical Sciences), and went abroad for medical internships in Cameroon and Nicaragua. She has always had a great interest in global health and humanitarian work. She organized the university's tropical medicine curriculum and works as a volunteer for Humanitas. After her clinical rotations in Enschede, she moved to Utrecht. During the final six months of her studies, she met the driven and dedicated researchers Arjan Bredenoord and André Smout, who supervised her during her master thesis in the Academic Medical Center in Amsterdam at the department of Gastroenterology and Hepatology. After obtaining her medical degree in October 2017, she started as a PhD candidate at the same department. For a period of three years, she combined clinical and laboratory studies focusing on esophageal motility disorders, which eventually resulted in this thesis. In the beginning of 2021, she returned to clinics as a resident not in training (ANIOS) at the departments of Internal Medicine and Gastroenterology and Hepatology at the St. Antonius Hospital in Nieuwegein. In her free time, Renske enjoys doing sports, preferably outside in nature. She lives together with Jasper in Utrecht. Starting in March 2022, they will take up another big adventure by cycling from Utrecht to Indonesia following the silk road.

DANKWOORD

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