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What's new on achalasia

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What's new on achalasia

Editorial

Achalasia, a primary motor oesophageal disorder

Peter Kahrilas

In recent years, the evaluation and management of the patient presenting with oesophageal complaints (e.g. dysphagia, regurgitation, chest pain, food impaction) has evolved considerably, with the advent of new diagnostic technologies and improved understanding of oesophageal physiology.

A number of novel techniques - high-resolution manometry, functional luminal imaging probe (FLIP) and intra-luminal ultrasound imaging - have improved our understanding of oesophageal function in health and disease. Several studies address the function of longitudinal muscle layer of the oesophagus in normal subjects and patients with motor disorders of the oesophagus.
Oesophageal electrical impedance recordings reveal abnormal transit in patients with diffuse oesophageal spasm, achalasia and patients with normal manometry.

These advances have led to more precise characterization of oesophageal motility and a management approach that is increasingly directed by differential phenotype. Some of these advances in investigation and diagnosis have improved treatment of oesophageal motility disorders and gastro-oesophageal reflux disease.

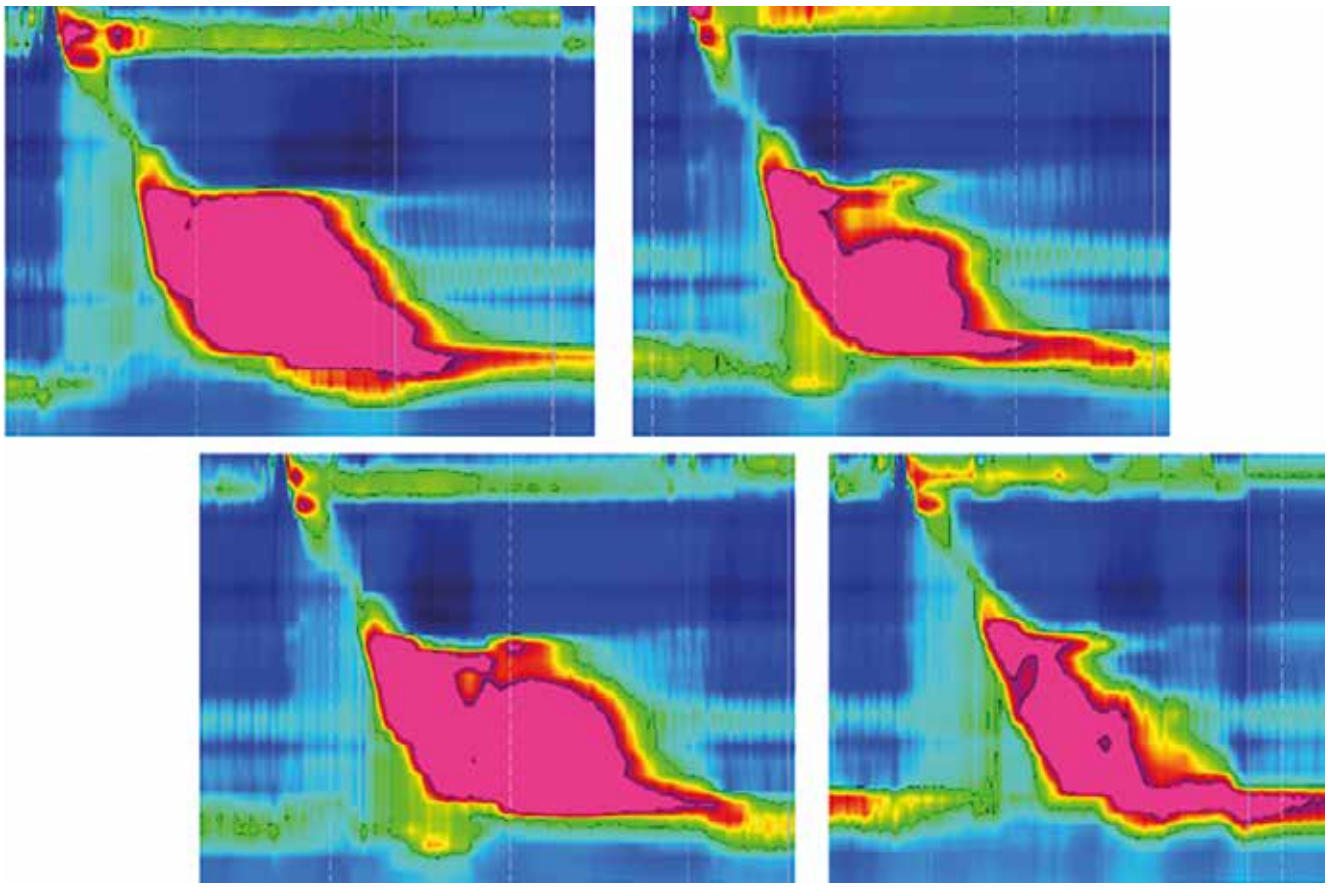
Achalasia is a relatively rare primary motor oesophageal disorder, characterized by absence of relaxations of the lower oesophageal sphincter and of peristalsis along the oesophageal body. As a result, patients typically present with dysphagia, regurgitation and occasionally chest pain, pulmonary complication and malnutrition.
Several studies have shown excellent long-term results of medical and surgical treatment of achalasia of the oesophagus. Novel pharmacologic strategies in the treatment of reflux disease are highlighted.

A case of spastic achalasia variant and 'blown-out myotomy'

Dustin Carlson

INTRODUCTION

Achalasia is a relatively rare primary motor esophageal disorder, characterized by absence of relaxations of the lower esophageal sphincter and of peristalsis along the esophageal body. As a result, patients typically present with dysphagia, regurgitation and occasionally chest pain, pulmonary complication and malnutrition. New diagnostic methodologies and therapeutic techniques have been recently added to the available tools for diagnosing and treating this devastating disease.



EGJ outflow obstruction with hypercontractility
IRP (median) 19 mmHg; DCIs 8000-24000; DLs 6-8s

Figure 1. HRM diagram

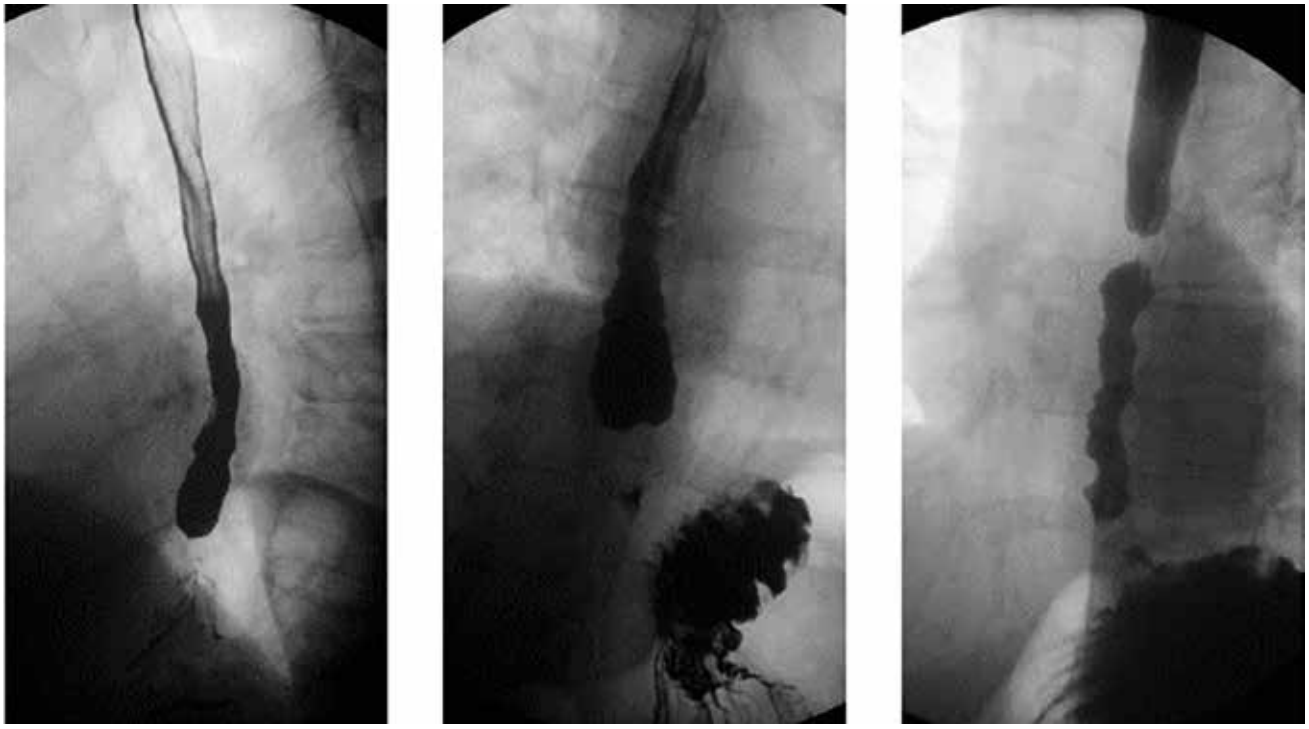


Figure 2. Oesophagram

THE CASE

A 58-year old female presented to the clinic with dysphagia and chest pain. Her dysphagia had gradually worsened over a period of 2–3 years and now involved both solids and liquids. She was initially seen at another hospital where a submucosal nodule in the oesophagus at 32 cm distant from incisors had been identified.

DIAGNOSTIC PROCEDURE AND MANAGEMENT

Oesophageal wall thickening (suspected submucosa layer) and an apparently tight oesophagogastric junction (EGJ) were observed on investigation by endoscopic ultrasound. High-resolution manometry (HRM) was then performed and EGJ outflow obstruction with hypercontractility was diagnosed. Median integrated relaxation pressure (IRP) was 19 mmHg, distal contractile integral (DCI) was 8000–24000 and distal latency was 6–8 seconds (Figure 1).

A complementary barium tablet oesophagram was done and was strongly suggestive of functionally

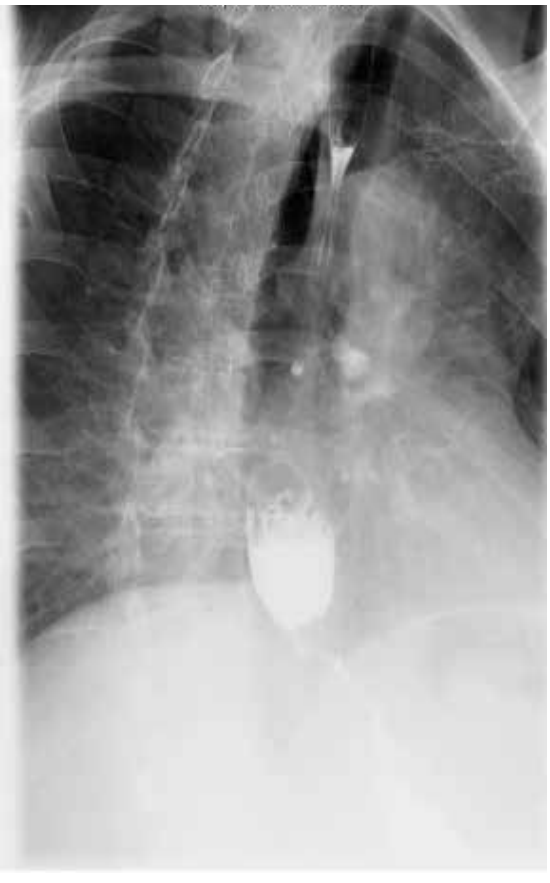


Figure 3. Endoscopy at year 5

significant EGJ outflow obstruction (EGJOO) (Figure 2). Based on these findings, a diagnosis of EGJOO with hypercontractility (achalasia-variant) was reached.

Management initially involved the use of the smooth muscle relaxant, isosorbide dinitrate. Like other medical treatments, nitrates may provide some symptomatic benefit but are not durable therapies and do not halt disease progression. In this patient, dysphagia persisted and, following an oesophagogastroduodenoscopy (EGD), botulinum toxin 100 IU was injected into the lower oesophageal sphincter (LES). However, this did not resolve symptoms of dysphagia. At this stage, peroral endoscopic myotomy (POEM) was decided upon. An advantage of POEM over laparoscopic Heller myotomy (LHM) is that it allows for a longer myotomy. In this patient, the procedure involved an anterior myotomy which extended 8 cm proximally from the EGJ, with a total length of 12 cm.

At follow-up after one year, the patient still complained of symptoms of dysphagia and chest pain, although these were subjectively rated as having improved by around 50%. HRM and barium tablet oesophagram were performed. Results of the HRM showed treated EGJOO and hypercontractility, with a median IRP of 18 mmHg, and DCI of 3000–8500. Over the course of the next four years, the patient had a manageable level of symptoms, did not experience any significant weight loss and did not have any difficulties in sleeping. She was prescribed smooth muscle relaxants and was treated with proton pump inhibitors for gastro-esophageal reflux disease (GERD).

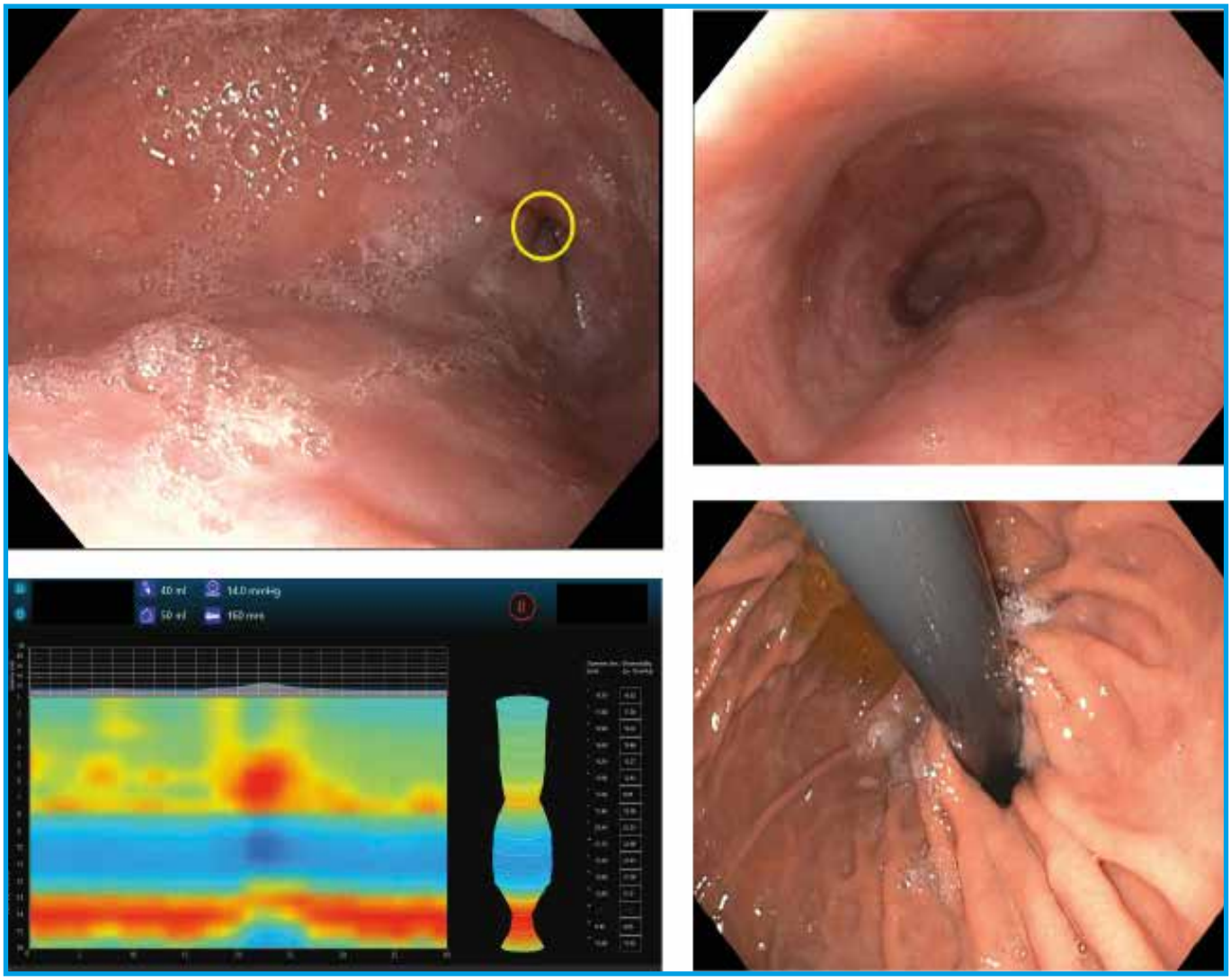


Figure 4. EGD and FLIP panometry at year 6

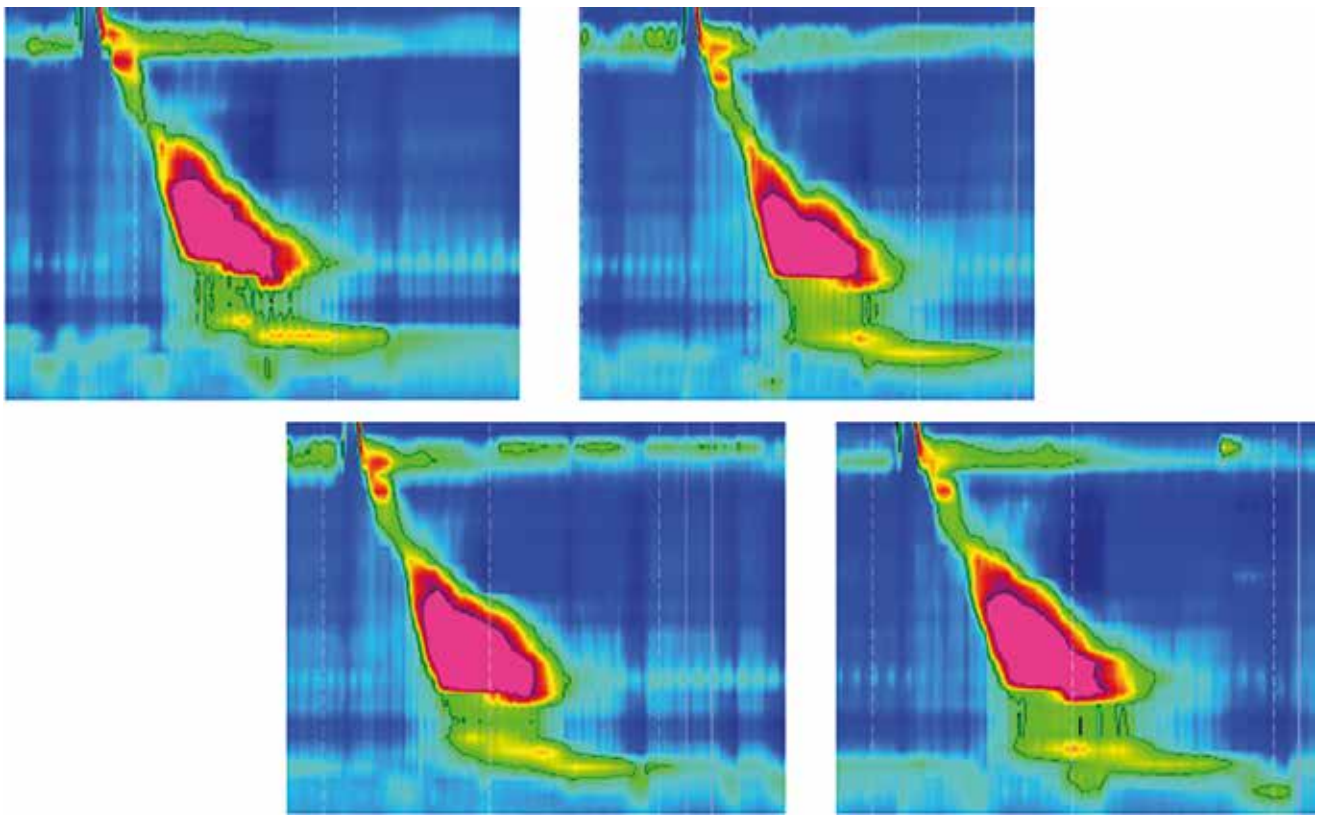
FIVE-YEAR FOLLOW-UP

However, new symptoms occurred at five years after the initial presentation, consisting of hiccups after meals and chest discomfort after eating, the description of which implied food items were being caught in the proximal oesophagus. Endoscopy suggested mild reflux oesophagitis with Los Angeles classification B (i.e. one or more mucosal breaks more than 5 mm long that do not extend between the tops of two mucosal folds) (Figure 3). HRM was again performed and hypercontractile oesophagus in the setting of previous myotomy, with distal peristaltic break and compartmentalized pressurization was identified. Median IRP was 14 mmHg and DCI was 3000-8800.

After a further year, the patient presented for an urgent visit in relation to her dysphagia. She reported dysphagia with most meals involving solid food and was following a liquid diet. The patient also described experiencing daily regurgitation, as well as occasional chest pain and epigastric pain. A barium tablet oesophagram was performed, which cleared after 2 minutes. EGD was performed with a functional luminal imaging probe (FLIP) and panometry (Figure 4).

HRM diagnosed normal motility in the setting of previous myotomy, with distal peristaltic break and compartmentalized pressurization; median IRP was 7 mmHg and DCI was 3400-6700 (Figure 5).

The patient was diagnosed as having spastic achalasia-variant treated with POEM with the subsequent development of pseudodiverticulum of the myotomy segment, or 'blown-out myotomy' (BOM). BOM is a possible cause for myotomy failure in achalasia.



Normal motility in setting of previous myotomy
(with distal peristaltic break and compartmentalized pressurization)
IRP (median) 7 mmHg; DCIs 3400-6700

Figure 5. HRM at year 6

CONCLUSIONS

Analysis of patients from the Northwestern Esophageal Center Achalasia Natural History Study undergoing HRM following LHM or POEM as therapy for achalasia has suggested that oesophageal myotomy to treat spastic achalasia, treatment with LHM, and a higher post-treatment IRP are more common in patients with a BOM. Increased wall strain, whether from residual spastic contractility, continued outflow obstruction from fundoplication, or an incomplete myotomy, may be the underlying mechanism of failure. One issue is that of the oesophageal myotomy length and whether this should this be extended or tailored. Another consideration is what is the most appropriate next step for this patient e.g. oesophagectomy or an alternative approach?

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Achalasia: what's new in pathophysiology and disease mechanism

Arjan Bredenoord

INTRODUCTION

Achalasia is a relatively rare esophageal motor disorder characterized by the absence of swallow-induced relaxation of the lower esophageal sphincter (LES) and by absence of peristalsis along the esophageal body. Consequently, the transit of food into the stomach is impaired and the patient typically experiences dysphagia. Other reported symptoms are: regurgitation of saliva or undigested food, respiratory symptoms (nocturnal cough, recurrent aspiration, and pneumonia), heartburn, and chest pain (1).

Achalasia can be subcategorized into different forms: primary or "idiopathic" and secondary achalasia, associated with Chagas' disease or with AAA (achalasia, Addison disease, and alacrima) syndrome, caused by mutations in the AAAS gene, which encodes a protein known as ALADIN (ALacrima Achalasia aDrenal Insufficiency Neurologic disorder). Pseudo-achalasia can be benign - that is consequent from fundoplication, gastric bypass, amyloidosis, sarcoidosis, trauma - or malignant. Primary achalasia is a rare disease, with mean incidence of 0.3–1.63 per 100 000 people per year in adults, with no significant difference between men and women, but with increasing incidence due to aging. Mean prevalence is about 10 per 100.000 people, increasing over time as expected for a chronic disorder with a low disease-related mortality rate. A Dutch study based on a database including over 4 million people (907 achalasia patients) reported that in the year prior to diagnosis 74% of patients was prescribed PPI and 26% anti-emetics and that in the first year after diagnosis median total direct medical costs for achalasia patients were € 2.283,00 (2).

DIAGNOSTIC EVALUATION

Esophageal manometry is the gold standard for the diagnosis of achalasia. Lack of peristalsis and partial or absent relaxation in response to swallowing are key criteria for the diagnosis. While in the past the LES was thought to be hypertensive in all patients, today it is well known that an elevated LES pressure is present in about 50% of patients only.

The introduction of high-resolution manometry (HRM) has improved the ability to diagnose achalasia and identify new variants. As compared to conventional manometry, HRM is more comfortable, quicker, more easily lectured, has better inter-observer and intra-observer reproducibility, and is less prone to movement artefacts.

The test is performed after an overnight fast using a solid-state catheter with 36 circumferential sensors located at 1 cm intervals. The probe is inserted trans-nasally, and is positioned in order to record from the pharynx to the stomach. Pressure, length and relaxation of the lower and upper esophageal sphincters are recorded. Esophageal body motility is assessed by 10 swallows of 5 ml of water, given at 30 seconds intervals. When the esophagus is dilated and sigmoid, it might be difficult to pass the catheter through the gastroesophageal junction, and fluoroscopic or endoscopic guidance may be necessary.

In 2008, Pandolfino et al. (3,4) in two different

articles proposed a classification according to the HRM manometric patterns of esophageal body contractions. This classification divides achalasia in to 3 subtypes (Figure 1):

• Type I: incomplete LES relaxation, aperistalsis and absence of esophageal pressurization.

• Type II: incomplete LES relaxation, aperistalsis and pan-esophageal pressurization in at least 20% of swallows.

• Type III: incomplete LES relaxation and premature "spastic" contractions (distal latency < 4.5 seconds) in at least 20% of swallows.

ESOPHAGOGASTRIC JUNCTION OUTFLOW OBSTRUCTION

Using HRM, a patient group was identified with EGS outflow obstruction.

Some of these patients have a variant or incomplete form of achalasia.

In some patients, the symptoms of EGJ outflow obstruction are similar to achalasia and respond to achalasia treatment, whereas in other patients the outflow obstruction disappear spontaneously (2).

No predictors of progression to achalasia were identified in these patients for long term achalasia development.

PATHOPHYSIOLOGY AND DISEASE MECHANISM

The pathophysiology of achalasia involves the degeneration of neurons of the esophageal myenteric plexus, which are needed for peristalsis of the smooth muscle of the esophageal body, as well as relaxation of the tonic LES. The etiology of this degenerative process, however, remains largely unknown. Detailed examination of resection specimens has shown infiltration of cytotoxic lymphocytes expressing activation markers. Perhaps some viruses such as varicella-zoster, human papilloma and herpes could be implicated in initiating an inflammatory reaction. The neurons producing nitric oxide are usually affected, while the cholinergic neurons are sometimes spared. As a consequence, the LES does not relax properly and it is often hypertensive (Figure 2) (5).

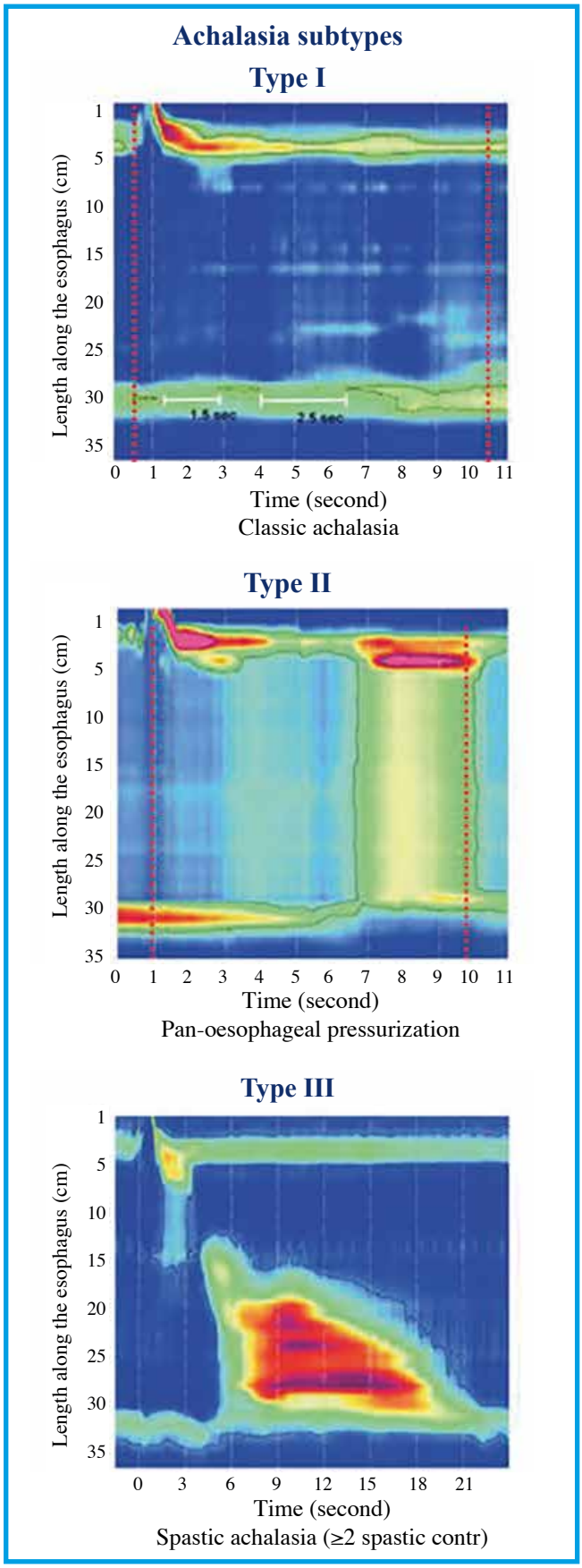

Figure 1. Achalasia manometric characterization (mod. from Pandolfino et al. Gastroenterology 2008)

There are other theories for the etiology of idiopathic achalasia. An autoimmune etiology has been suggested, with evidence of antibodies against myenteric neurons in the serum of achalasia patients (6-7). One study (7) showed 21.4% frequency of glutamic acid decarboxylase-65 antibody in patients with achalasia (versus 2.5% in control subjects), in the absence of diabetes or companion antibodies predictive of type 1 diabetes. This profile of autoantibodies suggests an autoimmune basis for a subset of primary achalasia.

A genetic association study (8), conducted in 1,068 achalasia cases and 4,242 controls, demonstrated that an eight-residue insertion at position 227-234 in the cytoplasmic tail of human leukocyte antigen haplotypes HLA-DQβ1 confers the strongest risk for achalasia. In addition, two amino-acid substitutions in the extracellular domain of HLA-DQα1 at position 41 and of HLA-DQβ1 at position 45 independently confer achalasia risk (Figure 3).

Another study (9) assessed whether single nucleotide polymorphisms (SNPs) in genes, mediating immune response and neuronal function, contribute to achalasia susceptibility. Three hundred 91 SNPs, covering 190 immune and 67 neuronal genes, were genotyped in an exploratory cohort from Central Europe (589 achalasia patients, 794 healthy volunteers - HVs). Twenty-four SNPs were validated in an Italian (160 achalasia patients, 278 HVs) and Spanish cohort (281 achalasia patients, 296 HVs). The rs1799724 SNP located between the lymphotoxin-α (LTA) and tumor necrosis-factor-α (TNFα) genes was significantly associated with achalasia.

The loss of myenteric neurons in the LES and the presence of lymphocytic infiltrates characterizes achalasia. The oligoclonal lymphocytic infiltrate within the LES of achalasia patients may represent the trace of an immune-inflammatory reaction triggered by HSV-1 antigens and the Th1-type cytokines released by the activated lymphocytes may contribute to establish the neuronal damage accounting for the clinical features of idiopathic achalasia.

Clark et al. studied the immunohistochemical characteristics of the inflammatory infiltrate within the myenteric plexus in patients with clinically early and end-stage achalasia. Using formalin-fixed tissue, they analyzed the immuno-histochemical features of the myenteric lymphocytes using antibodies that recognize B cells (CD20), T cells (CD3), T cell subsets (CD8), and the activation

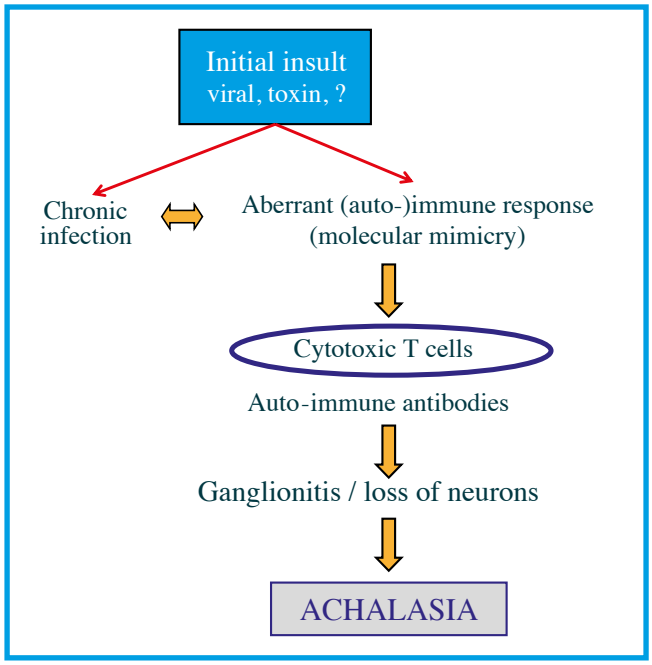

Figure 2. Pathophysiology of Achalasia (mod. from Boeckxstaens FNM 2018)

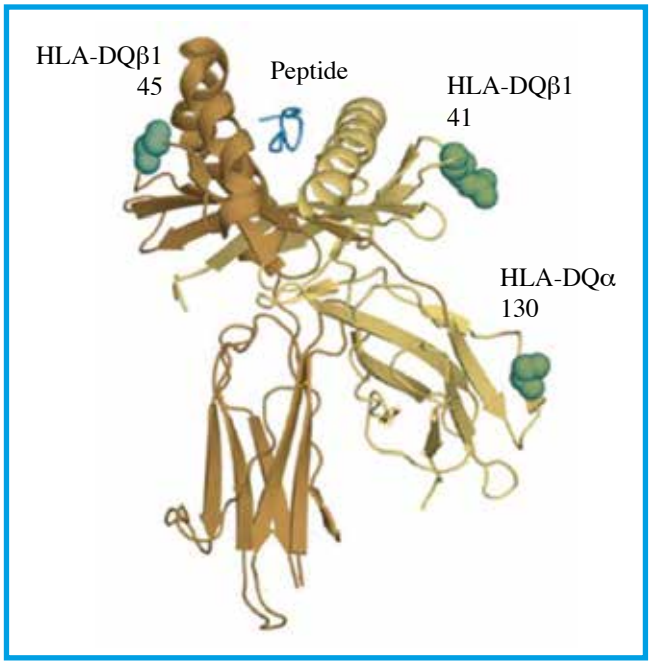

Figure 3. Structural model of the extracellular part of HLA-DQ (mod. from Gockel et al, Nat Genetics 2014)

state of T cell subpopulations (TIA-1 and granzyme B) in nine patients with clinically early achalasia who underwent esophagomyotomy and 13 patients with clinically end stage achalasia who underwent esophageal resection.

The majority of myenteric inflammatory cells in patients with achalasia were CD3-positive T cells, most of which were also CD8-positive, although the relative percentage of such cells appeared to decrease with disease progression. Furthermore, many of the CD3-positive/CD8-positive myenteric lymphocytes also expressed TIA-1, suggesting they are resting or activated cytotoxic T cells. The immunohistochemical demonstration of granzyme B in a subpopulation of these cells supports the contention that achalasia is an immune-mediated disease (Figure 4) (10).

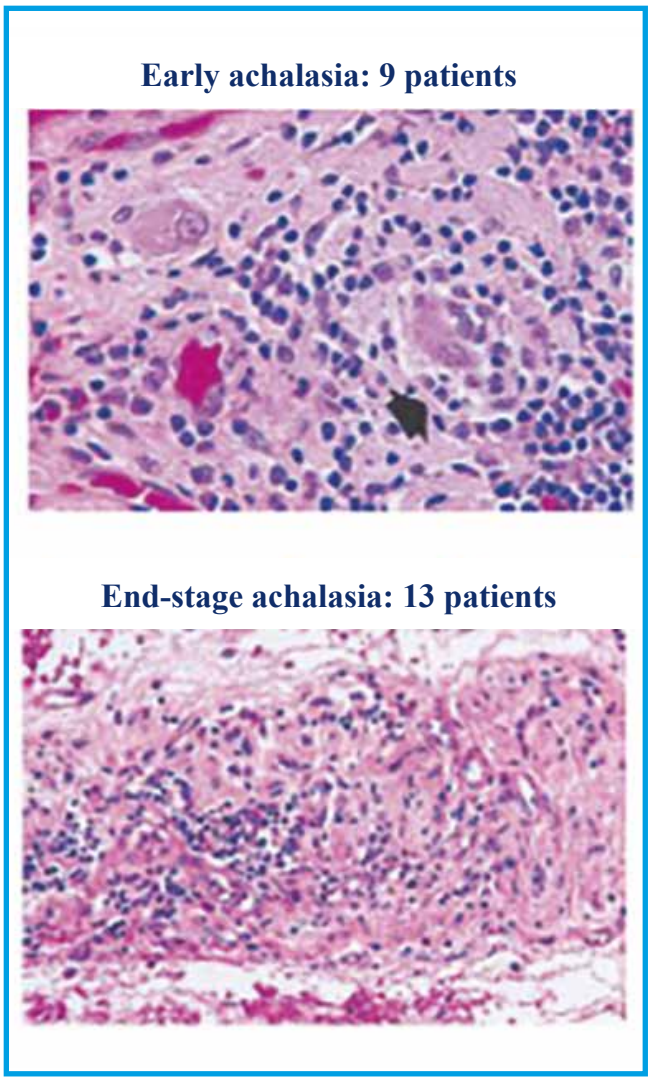

Figure 4. Hematoxylin and eosin stained section of the myenteric plexus from an esophageal resection specimen in a patient with clinically early achalasia and end-stage achalasia (mod. from Clark et al, 2000) Early achalasia - The myenteric plexus is infiltrated by inflammatory cells, predominantly lymphocytes. Lymphocytes are seen within the cytoplasm of one of the ganglion cells, so-called ganglionitis (arrow) End stage achalasia- Ganglion cells are not present, but there is an infiltrate of lymphocytes within a scarred myenteric nerve.

A few years later, Facco et al. showed that in the "early stage" of achalasia, the CD3+CD8+ T-lymphocyte infiltrate is associated with changes in the neurochemical phenotype of myenteric neurons, such as the reduction in nitric oxide synthase (NOS) containing neurons. However, neuromuscular function and nitrergic transmission have been reported to be altered in several models of intestinal inflammation as a consequence of NOS-immunoreactive fiber reduction even in the absence of neuronal loss. In fact, it is well accepted that cytokines released by infiltrating inflammatory cells can directly affect the activity and gene expression in neurons. Indeed, they observed that CD8+ T cells infiltrating the LES muscle of patients with achalasia cause a statistically significant increase in IL-1β, IFN-γ, and IL-2 levels as compared with healthy controls, corroborating the presence of cytokines potentially able to directly affect neuromediator expression and neuronal activity.

In addition, lymphocyte derived cytokines can influence the local production of neurotropic factors, instrumental in regulating the expression of neuromediators and supporting neuronal survival. As a result, specific neuromediators might be lost in the early stages of the inflammatory process as a direct effect of infiltrating CD3+CD8+ T-cell-derived cytokines, whereas in later stages of disease, neurons die as a consequence of the persistent exposure to inflammatory cytokines and the lack of neurotrophic factors. In summary, the lymphocytes infiltrating the LES of achalasia patients present three peculiar characteristics: increased CD3+CD8+ T lymphocytic infiltrate in the LES, a skewed T-cell receptor, and a strong reactivity toward HSV-1 antigens (11).

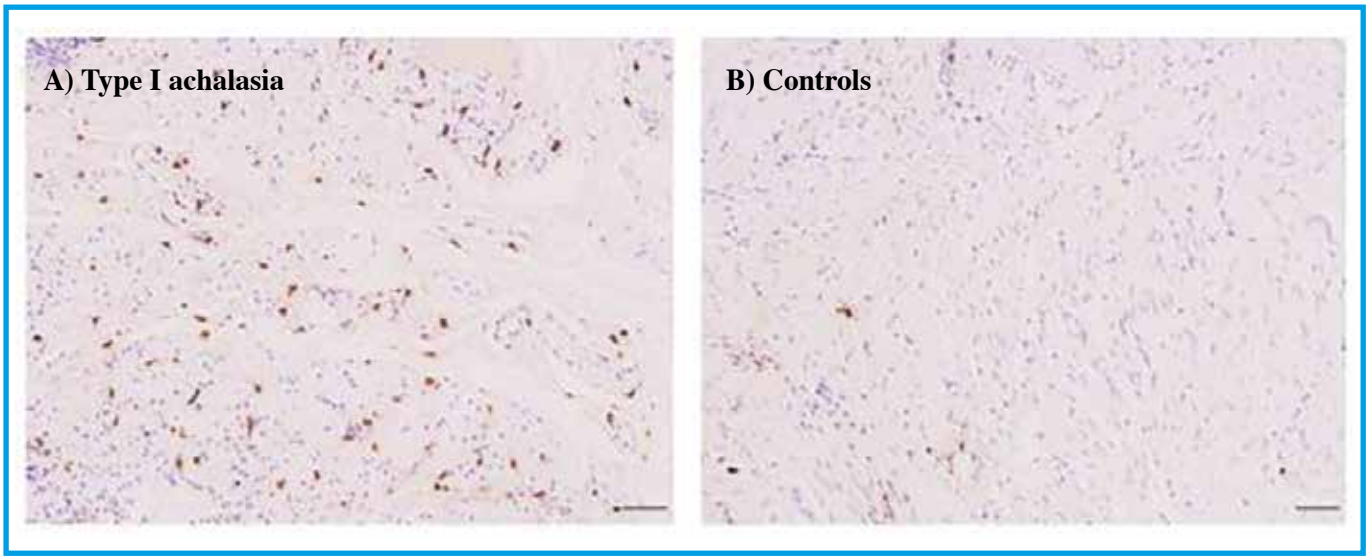

Figure 5. Anti-mast cell tryptase antibody binding in type I achalasia and control (mod. from Liu et al. Neurogastroenterol Motil 2019)

Zu Qiang Liu et al. (12) explored the role of mast cells in achalasia collecting information from 116 patients with achalasia who underwent peroral endoscopic myotomy between December 2016 and May 2017.

In patients with achalasia, mast cell infiltration in the LES muscle is increased, in association with loss of interstitial cells of Cajal and neuronal degeneration.

Mast cells may thereby play a crucial role in the development of achalasia (Figure 5).

NATURAL HISTORY OF ACHALASIA

In patients with untreated achalasia there is a progressive deterioration in the radiological parameters of the esophagus. After 5 years without any treatment, there is a significant increase in the diameter of the thoracic esophagus, with a mean "dilatation" rate of 6.1 mm/year. In addition, there is a significant decrease of the internal diameter of the esophagogastric junction, with a man 1 mm/year rate of "stenosis". The lower esophageal sphincter is hypertensive in all with an incomplete relaxation (13) (Figure 6).

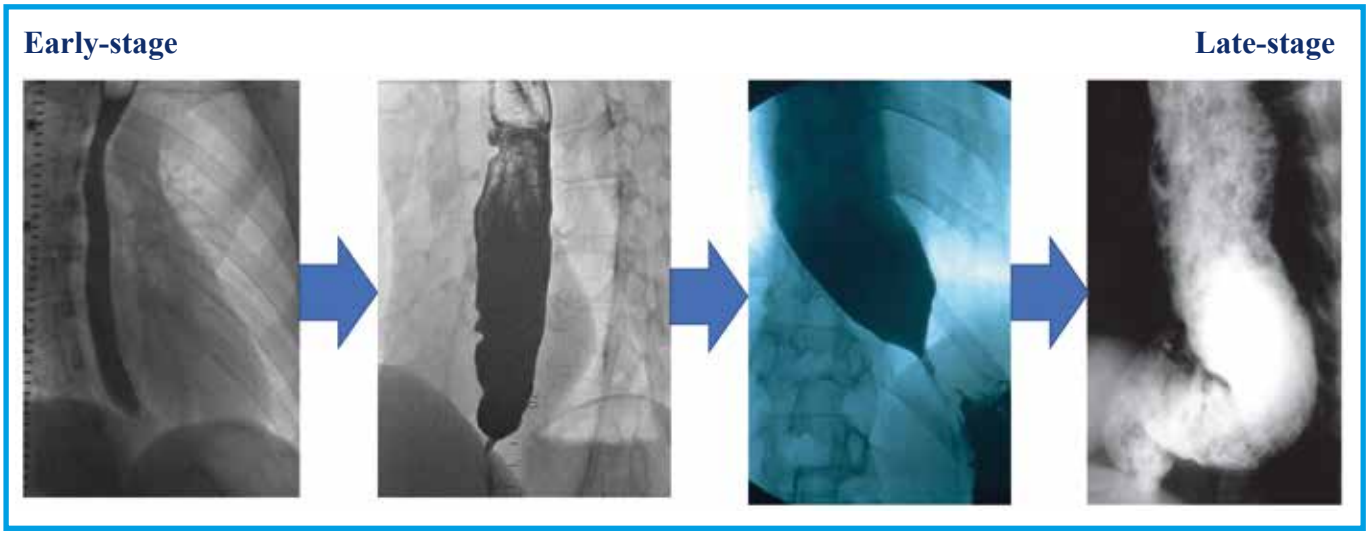

Figure 6. Evolutive Radiological Changes of the Esophagus in Patients with Achalasia (mod. from Csendes et al. Surg Today 2007)

Salvador et al. (14) tested the hypothesis that the three manometric patterns of esophageal achalasia represent different stages in the evolution of the disease and investigated whether manometric patterns change after Laparoscopic-Heller-Dor (LHD). The study population consisted of 511 patients whose demographic and clinical data showed that those patients with pattern III had a shorter history of symptoms, a higher incidence of chest pain, and a less dilated gullet. (Figure 7).

All patients with a sigmoid-shaped mega-esophagus had pattern I achalasia. One patient with a diagnosis of pattern III achalasia developed pattern II at a follow-up manometry before surgery. At a median follow-up of 30 months, the outcome of surgery was positive in 479 patients (91.7%).

All patients with pattern I preoperatively had the same pattern after LHD, whereas more than 50% of patients with pattern III before treatment showed pattern I or II after surgery.

This study supports the hypothesis/theory that the different manometric patterns represent different stages in the evolution of the disease-where pattern III is the earliest stage, pattern II an intermediate stage, and pattern I the final stage.

CONCLUSION

This article shows that patients with achalasia have a genetic predisposition. Some viruses such as varicella-zoster, human papilloma and herpes have been implicated in initiating an inflammatory reaction and aberrant autoimmune response. The affected neurons produced nitric oxide and, as a consequence, the LES does not relax properly.

The introduction of high-resolution manometry has improved the ability to diagnose achalasia and identify new variants. The Chicago Classification is a useful tool to define the clinically relevant phenotypes of achalasia.

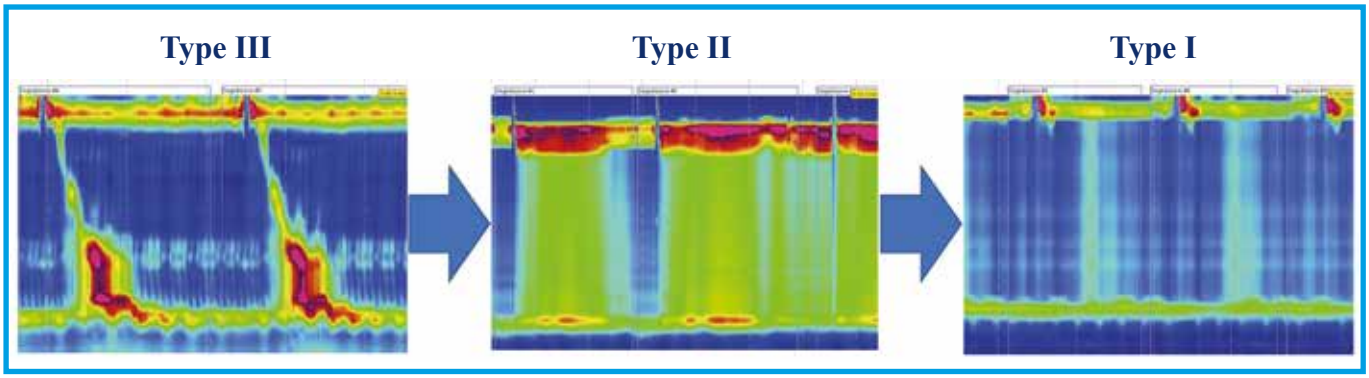

Figure 7. High-resolution manometry picture of achalasia. Evidence of a continuum "The evolutive pattern theory". (mod. from Salvador et al., Dig Liver Dis 2018)

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What's New in Diagnosis and Treatment

John E Pandolfino

In recent years, the evaluation and management of the patient presenting with oesophageal complaints (e.g. dysphagia, regurgitation, chest pain, food impaction) has evolved considerably, with the advent of new diagnostic technologies and improved understanding of oesophageal physiology.

These advances have led to more precise characterisation of oesophageal motility and a management approach that is increasingly directed by differential phenotype. Some of these advances in the investigation, diagnosis and treatment of oesophageal motility disorders and gastro-oesophageal reflux disease (GERD) are summarized here.

DIAGNOSIS OF OESOPHAGEAL MOTILITY DISORDERS

The Chicago Classification (CC) of oesophageal motility disorders, which is based on a hierarchical algorithm for the analysis of clinical high-resolution manometry (HRM) studies (Figure 1), is now firmly ensconced in daily practice, with the most recent update (v3.0) published in 2014 (1). The CC is based upon the integrated relaxation pressure (IRP), the distal contractile integral (DCI), and the distal latency, with hierarchical analysis of HRM beginning at the oesophagogastric junction and proceeding proximally. The first assessment of oesophageal motility is whether or not oesophagogastric junction outflow obstruction (EGJOO) is present as defined by the IRP. The classic disease of outflow obstruction is achalasia, which is defined by impaired lower oesophageal sphincter relaxation and which occurs as several disease phenotypes: type I achalasia (without peristalsis), type II achalasia (without peristalsis and with pan-oesophageal pressurisation), type III achalasia (with premature distal oesophageal contractions), or with preserved peristalsis (outlet obstruction). Physiological testing has also revealed other syndromes that do not meet the diagnostic criteria for achalasia but that involve obstructive physiology that may also benefit from treatments formerly reserved for achalasia.

Motility pattern disorders other than achalasia or EGJOO that are not encountered in control subjects are distal oesophageal spasm (normal mean IRP and ≥20% of premature contractions) (Figure 2); jackhammer (hypercontractile) oesophagus (≥20% of swallows with a DCI >8000 mmHg·s·cm and normal latency) (Figure 3) and absent contractility (normal mean IRP and absent peristalsis). The CC also considers borderline (minor) motor abnormalities seen in asymptomatic controls (Figure 4).

In the previous version of the CC, five minor peristaltic abnormalities were recognized. However, these have now been simplified to just two: ineffective oesophageal motility (≥50% ineffective swallows, DCI<450 mmHg·s·cm), which can be severe or mild and is not consistently related to disease states or symptoms and may be seen in asymptomatic healthy individuals (Figure 5), and fragmented peristalsis (≥50% fragmented contractions with DCI > 450 mmHg·s·cm).

Although HRM oesophageal pressure topography interpreted by the Chicago Classification is the gold standard to evaluate oesophageal motility, equivocal or conflicting findings may require supporting evidence of functionally significant EGJOO. This involves ancillary tests to elicit abnormal function.

such as the timed barium tablet oesophagram, which represents an important complementary diagnostic. A positive oesophagram is strongly supportive of functionally significant EGJOO and a completely normal result means a diagnosis of achalasia is unlikely. Anatomy and bolus retention patterns may inform aetiology and predict potential response to therapy. An oesophagram may also be critical in helping predict true EGJOO.

Another investigative approach for clarifying the significance of EGJOO is use of the functional luminal imaging probe (FLIP) device, which examines oesophageal motor response to distension and provides complementary data with regard to EGJ function and oesophageal body motor function. FLIP measures the distensibility of the EGJ outflow during volumetric distention via a transoral probe with impedance electrodes within a compliant bag and can be used to calculate an EGJ distensibility index (mm^2/mmHg) (10).

The possible advantage of FLIP over HRM is that it measures sphincter opening, which determines the

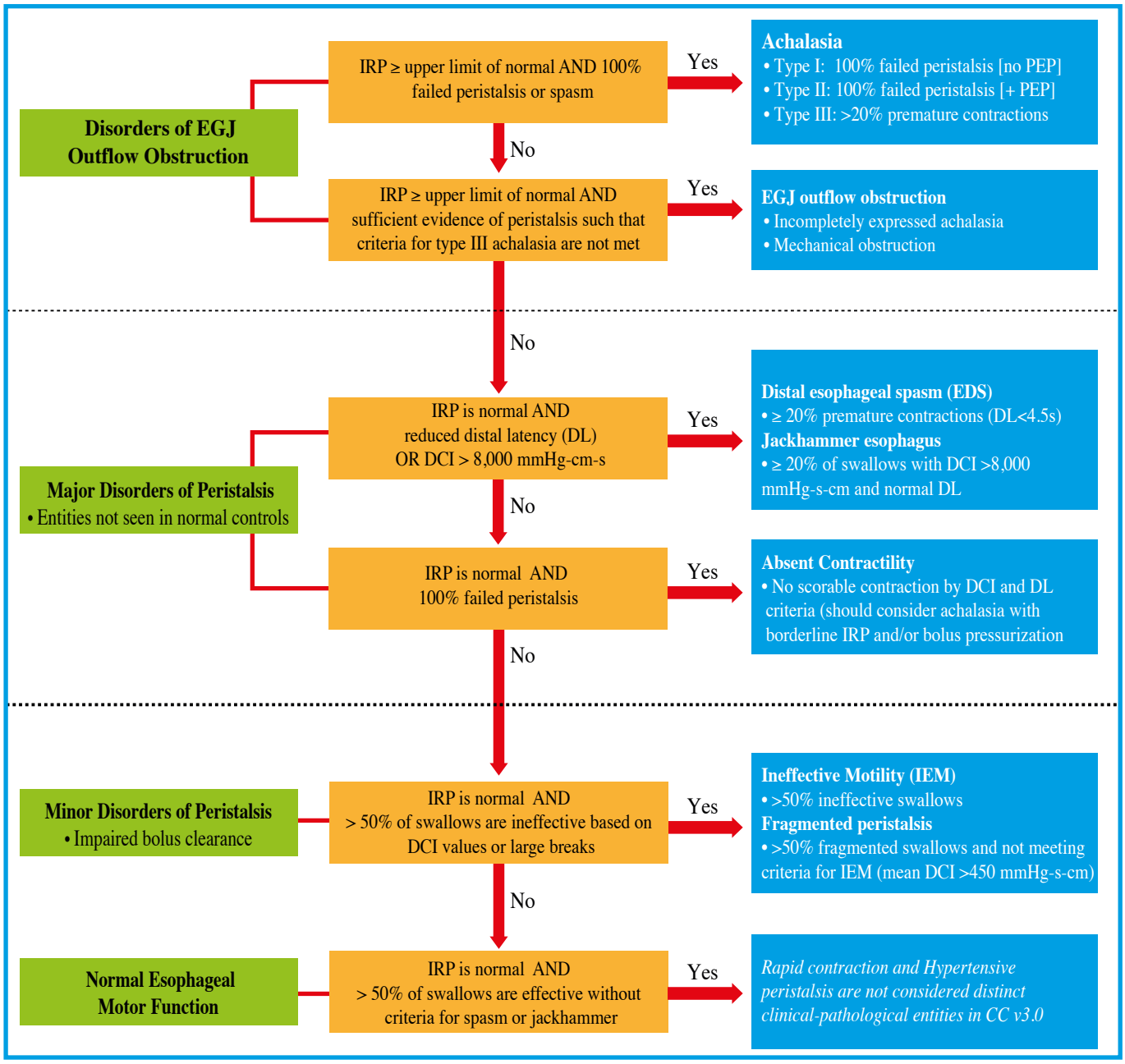


Figure 1. Chicago Classification 3.0

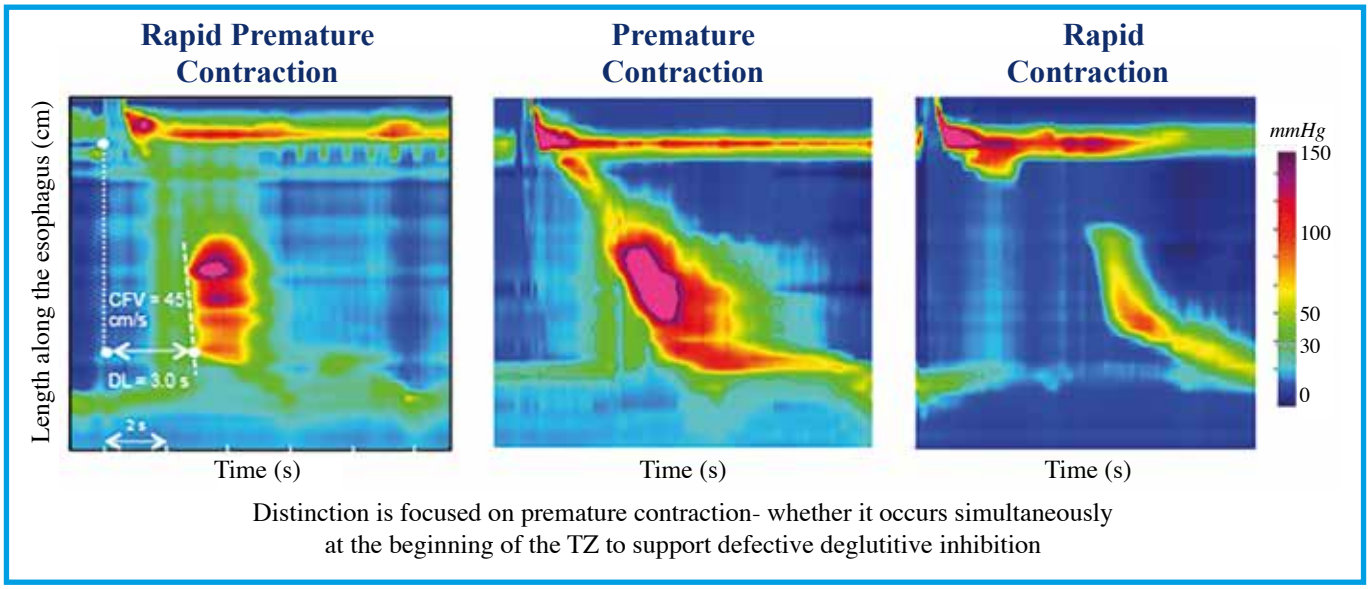


Figure 2. Distal Esophageal Spasm. Defining Relevant Phenotypes

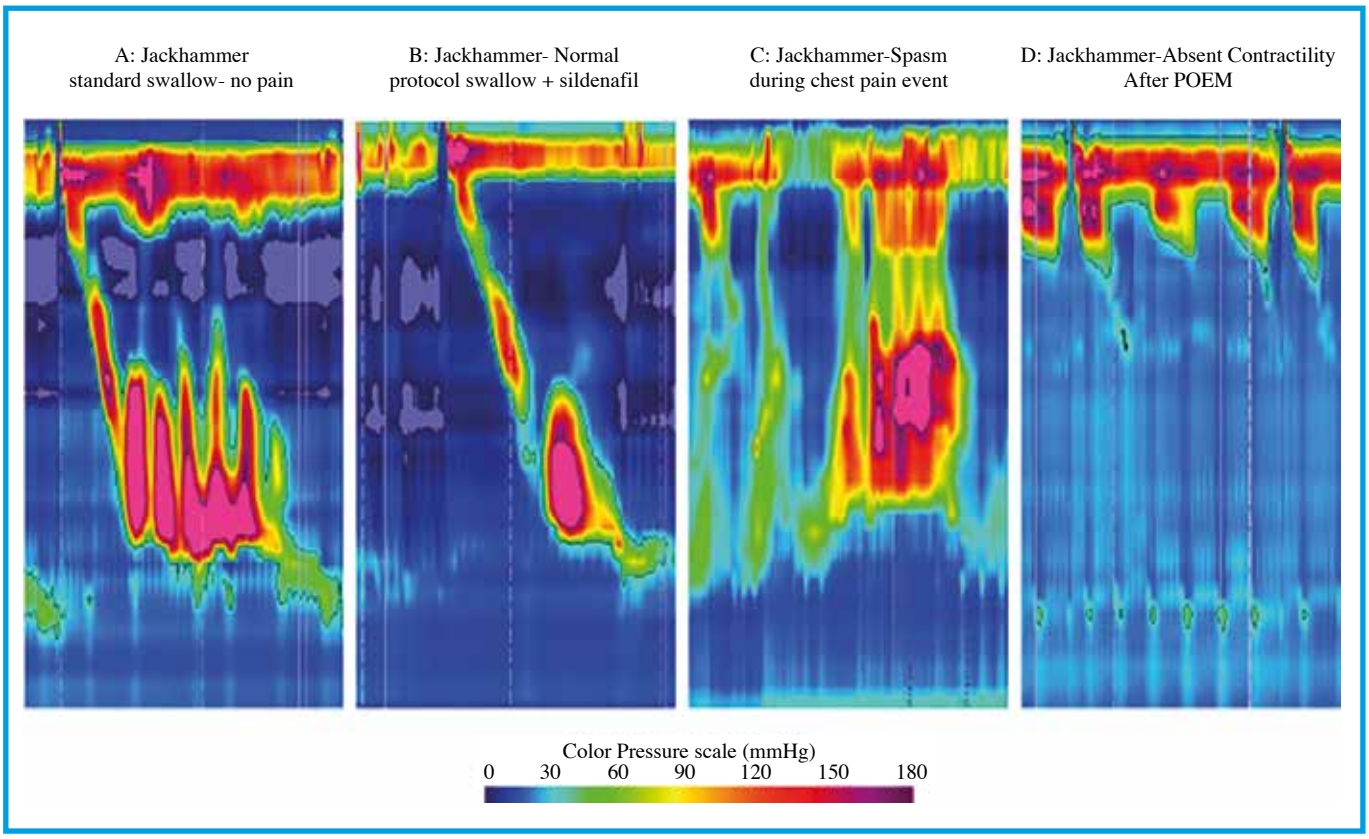
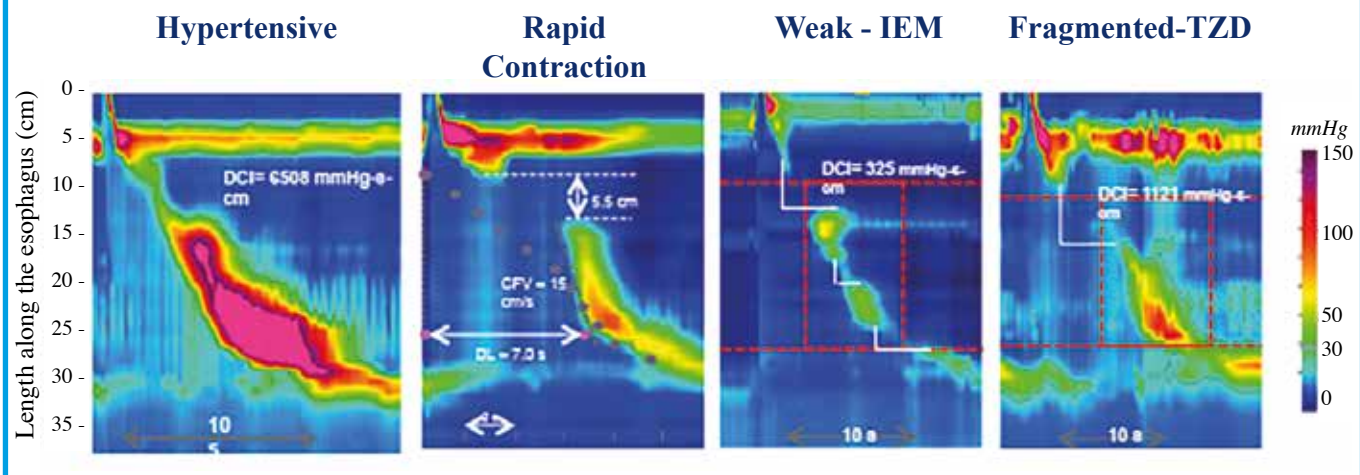


Figure 3. Jackhammer Esophagus

volume of bolus flow through the EGJ sphincter, whereas HRM measures sphincter relaxation. The FLIP device can also be used to measure oesophageal motility during endoscopy via panometry, which involves the secondary processing of FLIP data into topographic plots of oesophageal regional diameter changes versus time. Oesophageal contractility not observed with HRM can be detected in patients with achalasia using FLIP topography, which may represent variations in pathophysiology, and could have implications for additional subclassification of achalasia phenotypes (1).



- Probably just a normal variant outside of severe IEM and some transition zone defects.
- Rapid contractions with borderline DL values should be watched closely for progression and simultaneous contractions after the swallow may be reactivity to retained bolus

Figure 4. Borderline Motor Abnormalities seen in asymptomatic controls

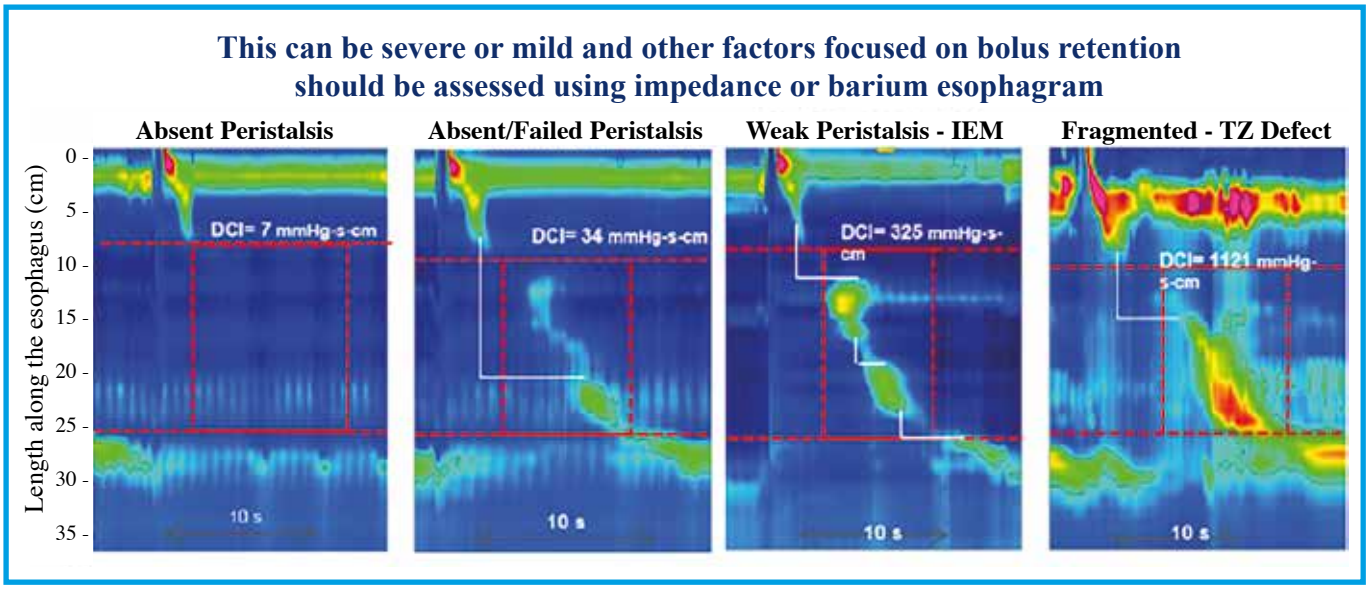


Figure 5. Ineffective Esophageal Motility. Assessing Integrity and Contractile Vigor

For example, a unique contractile pattern of repetitive retrograde contractions has been observed in patients with distal oesophageal obstructive physiology and only rarely in asymptomatic controls (2).

This pattern was first described in type III achalasia, and subsequently reported in patients with non-spastic achalasia, jackhammer oesophagus, oeosinophilic oeosophagitis, reflux, and secondary hypercontractility in post-fundoplication dysphagia. It has been proposed that these repetitive retrograde contractions may be indicative of ganglionic neural imbalance and motility of a spastic-type in the distal oesophagus. FLIP may be useful when HRM is difficult to perform.

AMBULATORY REFLUX MONITORING FOR DIAGNOSIS OF GASTRO-ESOPHAGEAL REFLUX DISEASE

Ambulatory pH monitoring has been in use for many years to detect and/or confirm abnormal

levels of acid reflux in the oesophagus. Reflux testing should be performed after cessation of proton pump inhibitor (PPI) therapy in patients with a low likelihood of GERD. In this setting, testing can be either catheter-based pH-monitoring, wireless pH-monitoring or pH-impedance monitoring. Catheter-based pH monitoring can be uncomfortable and inconvenient for patients. The wireless Bravo capsule monitoring system improves patient tolerability, avoids issues of catheter displacement and allows for prolonged monitoring of oesophageal pH over a 48 hour period. It also allows pH monitoring both on and off PPI therapy (9). Impedance monitoring detects reflux events regardless of their pH and measures the amount of time refluxed material remains in contact with the oesophageal mucosa and the distance above the lower oesophageal sphincter to which the refluxate enters the oesophagus. Analysis of impedance pH data by calculating the post-reflux swallow-induced peristaltic wave index and the mean nocturnal baseline impedance

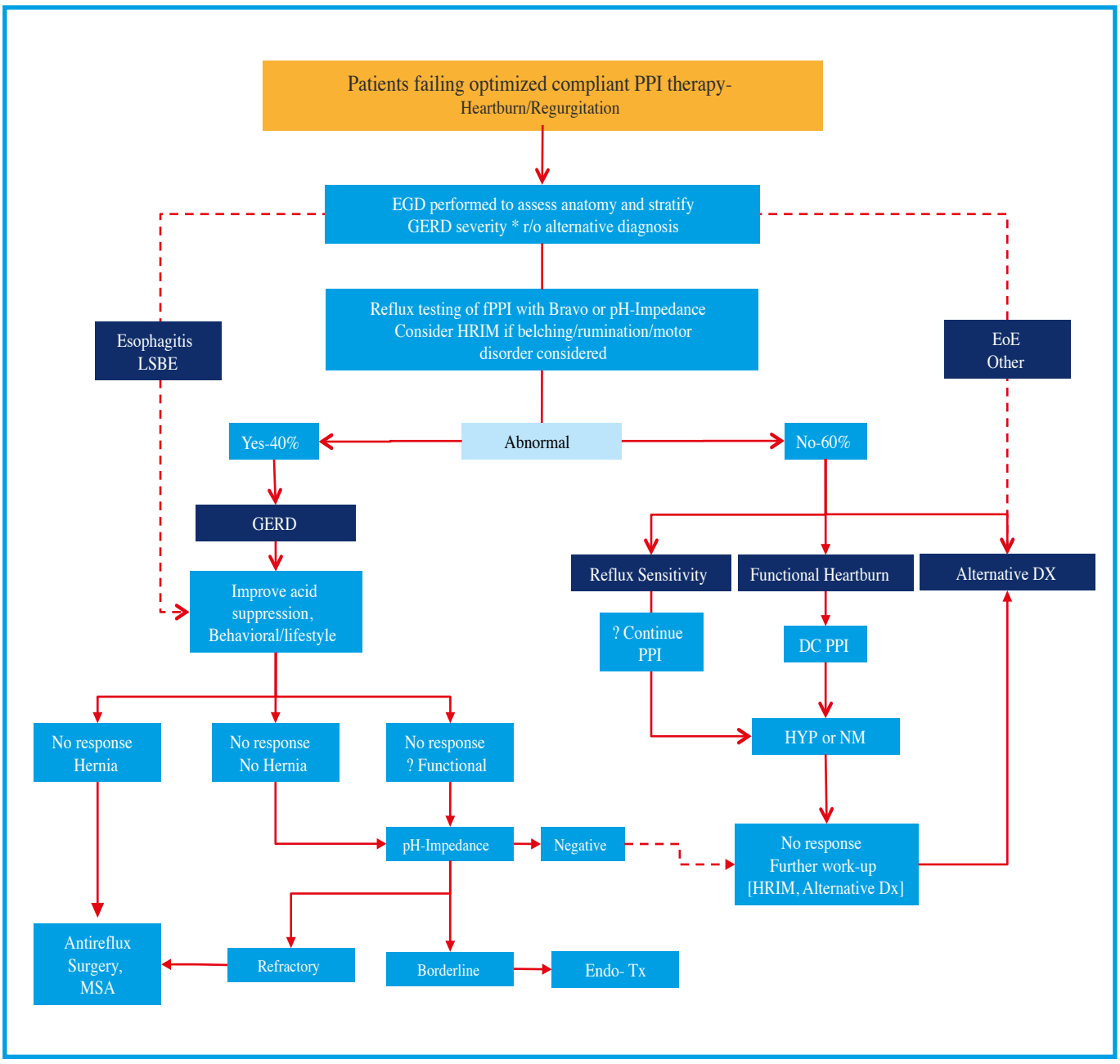
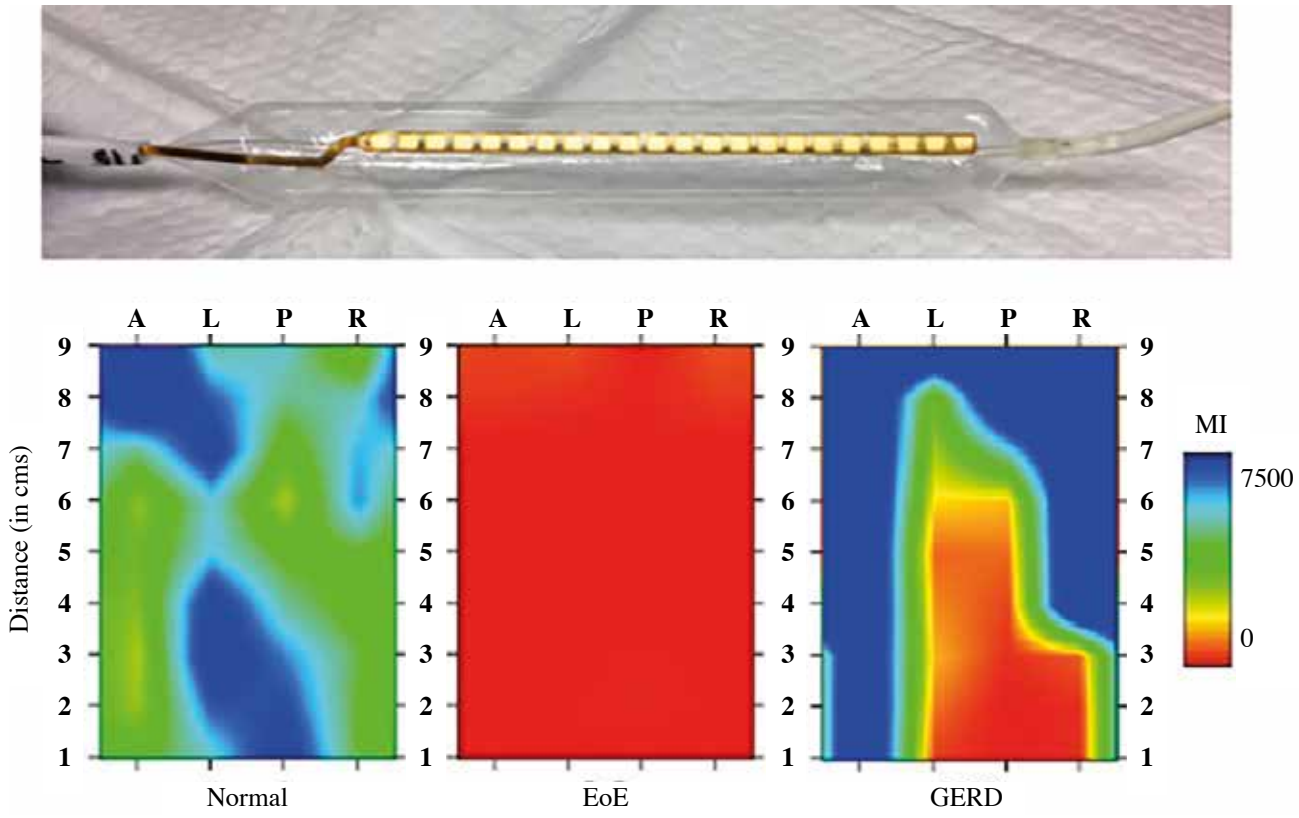


Figure 6. Phenotyping GERD based on EGD and reflux testing



MI pattern along the esophagus was significantly different (p<0.01) between GERD, EoE and normal subjects

Figure 7. Mucosal Integrity. Evolving the technology to improve outcomes.

can increase the accuracy diagnosis of patients with reflux disease, compared with data only based on pH values (3).

In patients with a high likelihood of GERD and persistent symptoms, pH-impedance monitoring should be performed on treatment. Reflux testing can be used with oesophagogastric duodenoscopy (EGD) to phenotype patients with GERD who fail on PPI therapy (Figure 6).

Recently, a balloon mucosal impedance (MI) catheter system that instantly detects changes in oesophageal mucosal integrity during endoscopy over an extended segment of the oesophagus has been developed (Figure 7).

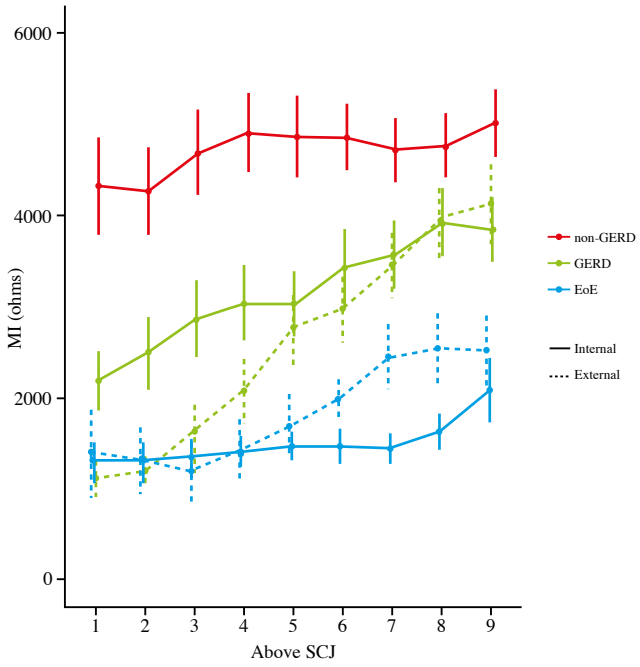
In a prospective study of 69 patients undergoing EGD with or without wireless pH monitoring, the MI pattern along the oesophageal axis was significantly different between patients with GERD, oeosinophilic oesophagitis, and non-GERD, with patients with GERD having a distinct pattern of low MI values in the distal oesophagus and normalised values in the proximal oesophagus (11) (Figure 8).

The system was also safe with just one patient reporting an adverse event (mild chest pain after the procedure).

TREATMENT OPTIONS FOR ACHALASIA AND OTHER OESOPHAGEAL MOTILITY DISORDERS

Treatment options for achalasia include medical treatment (nitrates, calcium channel blockers [CCBs] or phosphodiesterase inhibitors), Botulinum toxin injection, pneumatic dilation, laparoscopic Heller myotomy (LHM) and peroral endoscopic myotomy (POEM). There is no convincing evidence that medical treatment is effective for symptomatic relief in adults with achalasia, while Botulinum

Mean MI and SE over channels from distal to proximal esophagus (1 to >9) by diagnosis group in both internal (solid line) and external cohorts (dotted line).



Receiver operating characteristic analysis of intercept and slope of balloon MI measurements along the esophageal axis for diagnosis of GERD, EoE, and non-GERD

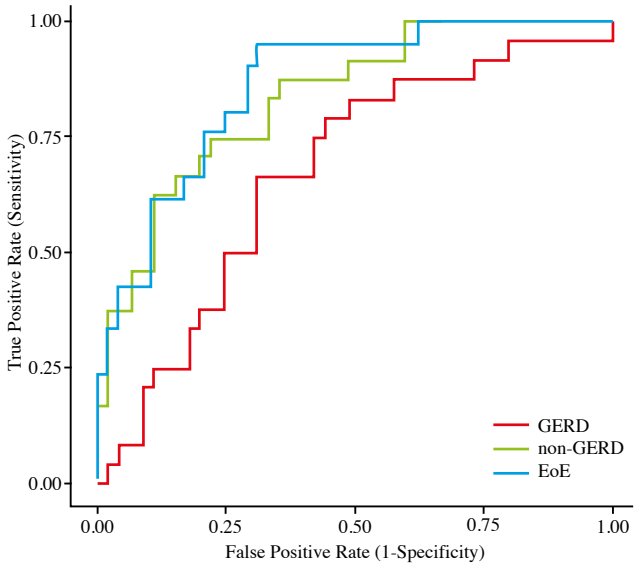


Figure 8. Mucosal Integrity. Evolving the technology to improve outcomes.

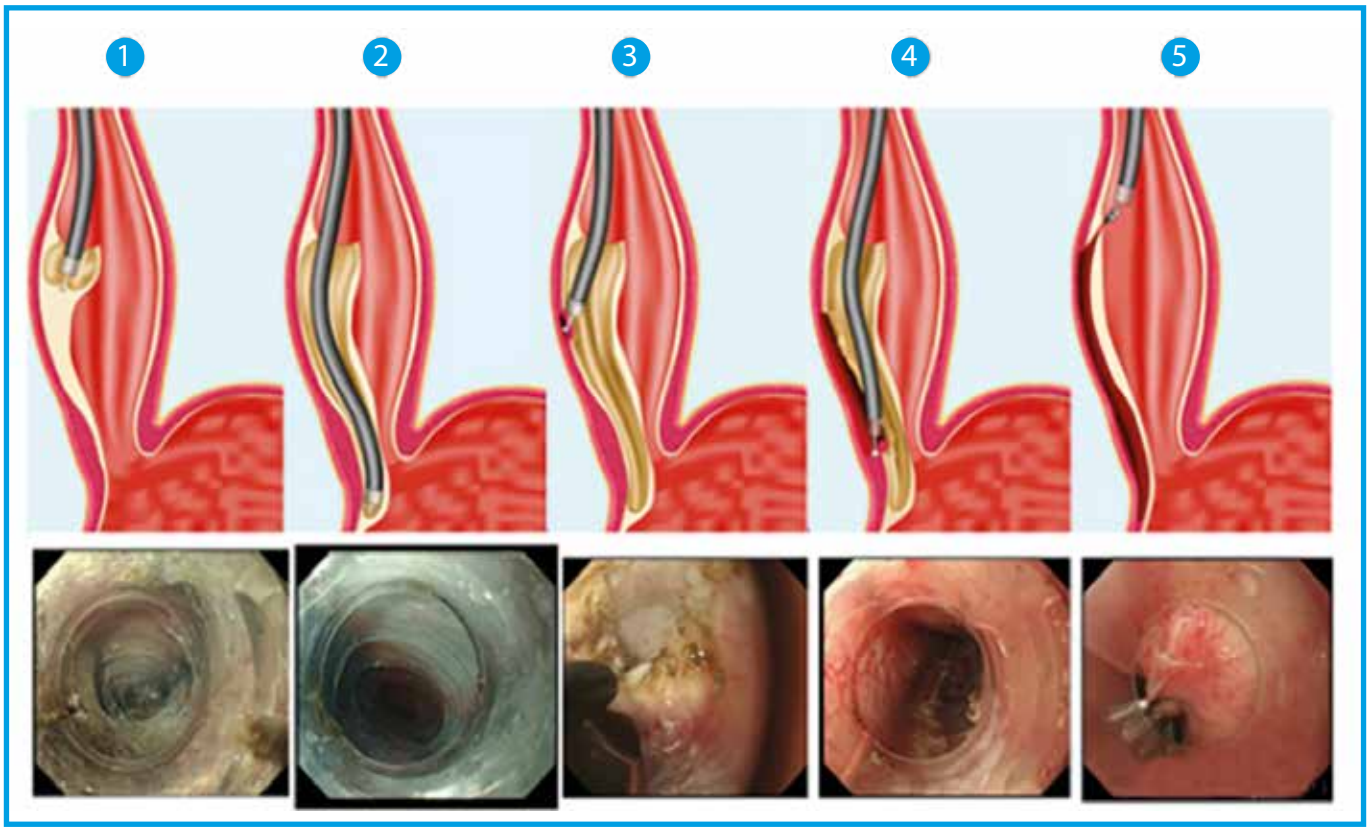


Figure 9. Steps of POEM procedure

toxin injection should be limited to patients unfit for surgery or as a bridge to more effective therapies, such as surgery or endoscopic dilation.

Peumatic dilation is aimed at reducing the lower oesophageal sphincter pressure in achalasia and reducing the resistance to bolus flow with consequent improvement in symptoms and is effective, although success rates decline over time and retreatment may be required.

POEM is a minimally invasive endoscopic procedure, involving a calibrated myotomy of the oesophageal circular muscle, the development of which has been especially relevant given that obstructive physiology may now be recognized as a primary target of therapy (Figure 9).

In the POEMA trial, patients with newly diagnosed achalasia and an Eckardt score >3 who had not undergone previous treatment were randomized to receive POEM (n=67) or pneumatic dilation with a 30-mm and a 35-mm balloon (n=66).

The primary outcome of treatment success was defined as an Eckardt score ≤3 and the absence of severe complications or re-treatment at the 2-year follow-up. This was achieved by a significantly higher proportion of patients in the POEM group compared with the pneumatic dilation group (92% vs 54%, a difference of 38% (95% CI, 22%-52%; p<0.001)(12).

Although LHM is the current standard management for type III achalasia, POEM may be superior because it allows for a longer myotomy. In a retrospective study of patients who underwent POEM (n=49) or LHM (n=26) for type III achalasia, clinical response was significantly higher in the POEM cohort (98.0% vs 80.8%; p=0.01).

Patients treated with POEM also had significantly shorter mean procedure times and significantly fewer adverse events (8).

Other studies have also shown POEM to be at least equivalent if not superior to LHM in terms of outcomes. In patients with non-achalasia oesophageal motility disorders, i.e. jackhammer oesophagus or distal oesophageal spasm, the severity of the motility disturbance should be assessed as well as the context in terms of presentation and anatomy. Further diagnostics may be considered e.g. reflux testing and PPI trial if GERD dominant, barium oesophagram or FLIP if dysphagia, endoscopic ultrasound with deep muscle biopsy). Medical management options include hyoscyamine, CCB calcium channel blockers CCB/nitrates, sildenafil, and Botulinum toxin, or tricyclic antidepressants if functional overlap is being considered.

Based on responses to medication, two distinct subgroups of jackhammer oesophagus have been identified: one with hypercontractility and normal distal latencies that improve upon treatment with an anticholinergic agent and the other with hypercontractility and short distal latencies that is unresponsive to both anticholinergic drugs and sildenafil (5).

POEM may also be considered for patients with non-achalasia oesophageal motility disorders. In 50 patients undergoing POEM for EGJOO (n=15), distal oesophageal spasm (n=17), and jackhammer oesophagus (n=18), technical success was achieved in all patients with a mean procedural time of 88 minutes and mean total myotomy of 15 cm (7).

Clinical success was achieved in 85% of distal oesophageal spasm/jackhammer oesophagus patients with median follow-up of 195 and 272 days, respectively. Nine (18%) adverse events occurred, of which 56% were adjudged mild and 44% moderate in severity. However, POEM should only be considered as a last resort after failure of conservative measures.

In patients with borderline motor abnormalities, symptoms of dysphagia, chest pain, regurgitation and food impaction should be assessed, with particular attention to abnormal retention/regurgitation, strain/stress on the oesophageal wall and hypersensitivity/perception if GERD mediated.

The underlying process (GERD/hypersensitivity) should be treated with focus on lifestyle modification and cognitive behavioural therapy.

Promotility agents are of limited value and neuromodulators may be a more useful treatment approach shows the management approach to patients with esophageal complaints (Figure 10).

TREATMENT OF PATIENTS WITH GERD

Patients with PPI-refractory GERD or PPI intolerance

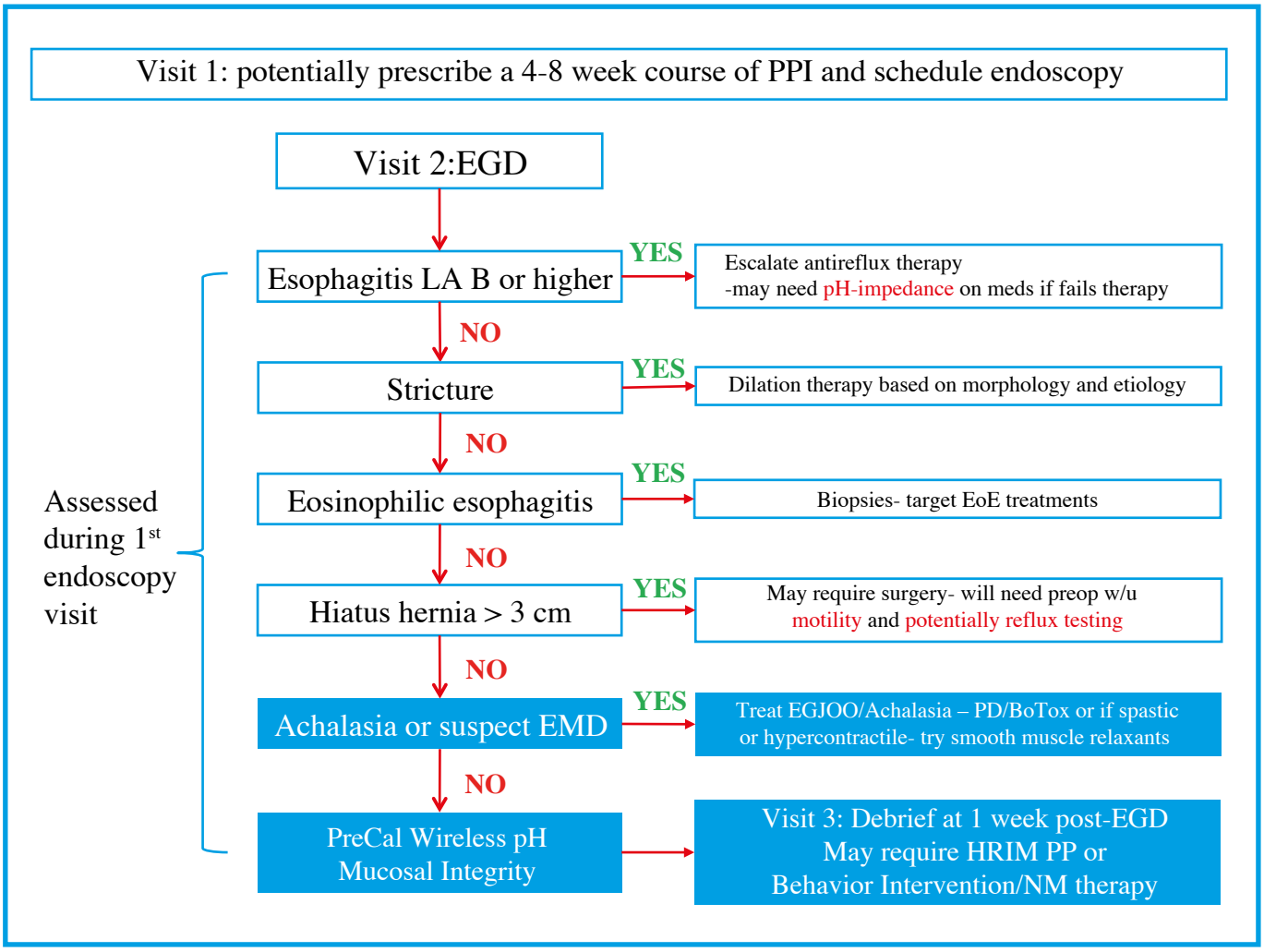


Figure 10. Approach to patient with esophageal complaints

- *Dysphagia, Regurgitation, Chest pain, Food impactions*
- *Diff Dx: GERD, EoE, EMD/Achalasia- difficult to distinguish on history*

may be candidates for anti-reflux surgery to restore the anti-reflux barrier. The standard surgical approach is laparoscopic Nissen fundoplication (LNF).

This, however, is non-reversible, and can be associated with significant side effects. Repeat surgery may also be required. Removable magnetic sphincter augmentation (MSA) is an effective alternative treatment option for patients who have some lower oesophageal sphincter function. Benefits of this approach include a standardized device and procedure, no alterations to gastric anatomy, and normal lower oesophageal sphincter function.

However, disadvantages include the use of an implanted device, device migration and erosion into the oesophagus and dysphagia. Endoscopic intervention may be appropriate rather than surgery in a patient with proven pathologic reflux with heartburn or regurgitation despite previous PPI therapy, and in whom an endoscopy reveals no herniation. Endoscopic approaches, such as radiofrequency ablation energy, anti-reflux mucosectomy and transoral incisionless fundoplication, are less invasive than MSA but may not provide a durable response and durability and do not treat major anatomical issues.

Patients with non-erosive GERD may benefit from mucosal protection added to PPI therapy. In a double-blind trial, 154 patients with NERD were randomised to receive Esoxx, a hyaluronic acid-chondroitin sulphate based bioadhesive formulation,

or placebo in addition to standard-dose PPI treatment for 2 weeks (13).

The proportion of patients who achieved the primary endpoint of at least a 3-point reduction in the total symptom score was significantly higher in the Esoxx group versus placebo (52.6% vs 32.1%; $p<0.01$). Improvement in health-related quality-of-life was also significantly greater in the Essox group.

CONCLUSIONS

In summary, in patients with dysphagia and oesophageal motility disorders it is important to identify and target the primary abnormality. If lower oesophageal sphincter relaxation and opening is impaired, it is necessary to reduce outflow obstruction.

If disordered and hypercontractile contraction is present, reduce contractility, while if hypocontractility is identified, reduce offending triggers. Hypervigilance, hypersensitivity and reflux should always be considered and it may be necessary to modify diet and assess changes in body weight. Follow-up is mandated as these disease states are typically not cured and can progress. Similarly, in patients with GERD, the first step is to identify the primary abnormality to be targeted. This may be abnormal motility, abnormal anatomy, increased hypersensitivity, decreased tissue resistance, or hypervigilance and visceral anxiety.

Diet should be modified and weight loss encouraged. Treatments should begin with the least invasive approach and complementary treatments should not be considered a failure.

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