Oesophageal dysphagia: manifestations and diagnosis

Frank Zerbib and Taher Omari

Abstract | Oesophageal dysphagia is a common symptom, which might be related to severe oesophageal diseases such as carcinomas. Therefore, an organic process must be ruled out in the first instance by endoscopy in all patients presenting with dysphagia symptoms. The most prevalent obstructive aetiologies are oesophageal cancer, peptic strictures and eosinophilic oesophagitis. Eosinophilic oesophagitis is one of the most common causes of dysphagia in adults and children, thus justifying the need to obtain oesophageal biopsy samples from all patients presenting with unexplained dysphagia. With the advent of standardized high-resolution manometry and specific metrics to characterize oesophageal motility, the Chicago classification has become a gold-standard algorithm for manometric diagnosis of oesophageal motor disorders. In addition, sophisticated investigations and analysis methods that combine pressure and impedance measurement are currently in development. In the future, these techniques might be able to detect subtle pressure abnormalities during bolus transport, which could further explain pathophysiology and symptoms. The degree to which novel approaches will help distinguish dysphagia caused by motor abnormalities from functional dysphagia still needs to be determined.

Zerbib, F. & Omari, T. *Nat. Rev. Gastroenterol. Hepatol.* advance online publication 18 November 2014; doi:10.1038/nrgastro.2014.195

Introduction

Oesophageal dysphagia is defined as a sensation of difficult passage of solids or liquids in the oesophageal body. Oesophageal dysphagia is a remarkably common symptom; the most recent study in 2008 reported that up to 16% of a random sample of 1,000 healthy individuals from Sydney, Australia, had a history of some form of dysphagia at some time in their life,[1] with the incidence increasing with age.[2] Dysphagia is considered to be an important alarm symptom as it might be related to severe oesophageal disorders such as oesophageal carcinoma. However, the prevalence of serious organic disease is low[2] and most patients will eventually prove to have dysphagia related to benign obstructive disorders or motility disorders.

Clinical presentation

In a patient with swallowing complaints, a careful interview is mandatory to confirm dysphagia, to differentiate (as best possible) whether the dysphagia is of a predominantly oesophageal or oropharyngeal nature and to provide a first impression regarding the potential underlying mechanism or aetiology (Box 1). Dysphagia should not be confused with a globus sensation, which is defined, according to the Rome III definition, as a non-painful sense of a lump, a retained food bolus or tightness in the throat, which frequently improves with eating and is therefore not associated with dysphagia.[3] Similarly, dysphagia should be differentiated from dyspeptic symptoms such as early satiety or bloating in patients reporting a sensation of delayed food bolus in the epigastrium.

Distinguishing between whether dysphagia symptoms are due to a predominantly oropharyngeal or oesophageal body cause can be difficult. Oropharyngeal dysphagia symptoms usually occur immediately after swallowing and can be associated with various symptoms such as choking and coughing, drooling and nasal regurgitation. Oesophageal dysphagia is indicated when passage of the food bolus is delayed in the chest or epigastrium; however, the ability of an individual to accurately identify the location where a food bolus is sticking varies. Patients localizing the site of bolus hold up to the cervical area or mid-chest often do not prove to have a cause in this area, whereas those complaining of more distal dysphagia are accurate in 80% of cases.[4] Oesophageal dysphagia is also more often associated with heartburn, regurgitation and chest pain than oropharyngeal dysphagia.

Dysphagia symptoms in relation to ingestion of solids are widely considered to suggest a mechanical obstruction. Dysphagia that occurs in relation to both solids and liquids suggests an underlying oesophageal motility disorder. However, both our own clinical experience and a systematic study[5] have demonstrated that the utility of such a symptomatic differentiation seems to be limited. Therefore, an organic process must be ruled out with appropriate investigations in all patients presenting with dysphagia symptoms.

Taking a careful history can be helpful to provide cues for several organic disorders. Alcohol abuse and/or

Gastroenterology and Hepatology Department, Saint André Hospital, Centre Hospitalier Universitaire de Bordeaux, 1 Rue Jean Burguet, F-33075 Bordeaux, France (**F.Z.**). Medical Science and Technology, School of Medicine, Flinders University, Sturt Road, Bedford Park, SA 5042, Australia (**T.O.**).

Correspondence to: F.Z. frank.zerbib@chu-bordeaux.fr

Competing Interests
F.Z. is a consultant and speaker for Given Imaging. T.O. holds patents on pressure-flow analysis methods.

Key points

- An organic process must be ruled out by endoscopy in all patients presenting with dysphagia symptoms
- Eosinophilic oesophagitis is one of the most prevalent causes of dysphagia in adults and children
- Oesophageal biopsy samples should be obtained in all patients with unexplained dysphagia symptoms
- High-resolution manometry is the gold-standard investigation for diagnosis of oesophageal motor disorders
- According to the Chicago classification algorithm, major oesophageal motor disorders are achalasia, oesophagogastric junction outflow obstruction, diffuse oesophageal spasm, hypercontractile 'jackhammer' oesophagus and absent peristalsis
- Sophisticated investigations (for example integrated pressure impedance analysis and impedance planimetry) could reveal subtle abnormalities and help distinguish between neuromechanical dysfunction and functional dysphagia

Box 1 | Aetiologies of oesophageal dysphagia

Obstructive

Malignant strictures
- Adenocarcinoma
- Squamous cell carcinoma
- Extrinsic compression

Benign strictures
- Peptic stenosis
- Schatzki ring
- Oesophageal web
- Drug-induced stricture
- Caustic stricture
- Oesophagitis dissecans superficialis

Eosinophilic oesophagitis

Complications after surgery
- Postfundoplication
- Anastomosis stricture

Nonobstructive

Motility disorders
- Achalasia
- Diffuse oesophageal spasm
- Absent peristalsis
- Hypercontractile 'jackhammer' oesophagus
- Oesophagogastric junction outflow obstruction

Functional dysphagia

smoking are risk factors for oesophageal carcinoma. GERD-related dysphagia might be suspected if heartburn and/or regurgitation are present. Dermatological disorders might be associated with oesophagitis or strictures. Oesophagitis owing to an acid or caustic cause is fairly easy to diagnose. Oesophagitis of a drug-induced nature can occur in relation to use of NSAIDs, potassium chloride and bisphosphonates; however, it is more difficult to detect from a patient's history because of potential lack of awareness from physicians and patients.[6] A longstanding history of mild dysphagia in young adult males with atopic disorders and one or several episodes of food impaction is very suggestive of eosinophilic oesophagitis.[7] Specific and validated questionnaires such as EAT-10[8] and MDQ-30[9] can be used to assess the initial level of disability and monitor treatment progress in adults.

Dysphagia is also prevalent in the paediatric population and can lead to failure to thrive, feed refusal, choking and airway changes secondary to aspiration.[10] Premature and newborn babies with dysphagia might fail to demonstrate adequate progression to full oral feeding due to immaturity of the complex control mechanisms responsible for suck, swallow and breathing coordination.[11] Many of the typical causes of adult presentations of dysphagia might have an early-life onset and can therefore manifest in the paediatric population.[11] Examples of disorders for which dysphagia is a secondary symptom include neurological disease, GERD, atopic disease and primary motor disorders, particularly achalasia. Oesophageal dysmotility and dysphagia have a high prevalence in children who have undergone surgical repair for congenital abnormalities, including oesophageal atresia and diaphragmatic hernia.[11] Current knowledge in relation to upper gastrointestinal motility in the paediatric population has been the topic of an extensive review[11] and therefore will not be discussed further here.

Endoscopy

Upper gastrointestinal endoscopy enables direct visualization of the oesophagus (as well as the stomach and duodenum) and the opportunity to obtain oesophageal mucosa biopsy samples. Endoscopy is a crucial first-line investigation for evaluating patients for structural causes of oesophageal dysphagia. Endoscopy can easily identify tumours, compression by extrinsic structures, strictures, webs and mucosal inflammatory changes related to GERD (peptic oesophagitis and stenosis), as well as caustic and drug-induced stenosis frequently located at the level of mid-oesophagus. Endoscopy can also demonstrate the presence of a severe oesophageal motor disorder, such as achalasia, if oesophageal stasis in a dilated oesophagus associated with a 'spastic' (tight) oesophagogastric junction (EGJ) is present (Figure 1). An oesophagus with a 'normal' appearance in a patient with dysphagia should lead the endoscopist to search for subtle mucosal changes, such as mild oesophageal stenosis or Schatzki ring, which can be easily overlooked.[12] In our own experience, a slightly dilated oesophagus and/or a paucity of oesophageal contractions could also suggest the presence of an oesophageal motor disorder; however, early stage achalasia is frequently missed at endoscopy because the changes are subtle. Looking for endoscopic oesophageal features of eosinophilic oesophagitis such as concentric rings (trachealisation), exudates (white spots), furrows or oedema (Figure 1) is important.[13] However, as the endoscopic appearance of the oesophageal mucosa might be normal in 10–25% of patients with eosinophilic oesophagitis, oesophageal biopsies should be performed in all patients with unexplained dysphagia.[7,14] If sloughing of large fragments of oesophageal mucosa occurs during biopsy or after passage of the scope, oesophagitis dissecans is indicated,[15] which can be either idiopathic or secondary to various bullous skin disorders[16] and lichen planus.[17]

Fluoroscopy and timed barium transit

Videofluoroscopic examination of oesophageal transit (barium swallow) is usually performed with the patient

in the supine position and then upright. Visualization of a swallowed bolus as it is propelled along the oesophageal lumen can determine anatomical abnormalities (for example, oesophageal diverticuli), luminal narrowing and/or obstruction (stricture, webs and rings) and hiatus hernia. Achalasia and other motor abnormalities (such as diffuse oesophageal spasm, stasis due to peristaltic failure or EGJ obstruction) can be detected. However, an oesophageal manometry test (see later) enables better understanding and characterization of these anatomical abnormalities than videofluoroscopic examination. Semi-solid boluses, solid boluses and radio-opaque tablets can also establish oesophageal bolus transport function in relation to the increased work load (that is, with a solid bolus). The timed barium oesophagram test can assess passive drainage of the oesophagus in patients with achalasia. During this test, the height and maximum width of the barium column (above the EGJ 'bird's beak') are taken at 1, 2 and 5 min after ingestion of ~250 ml of liquid barium. This test determines how effectively the oesophagus empties, which is useful for measuring the success of therapy to improve oesophageal outflow.[18,19]

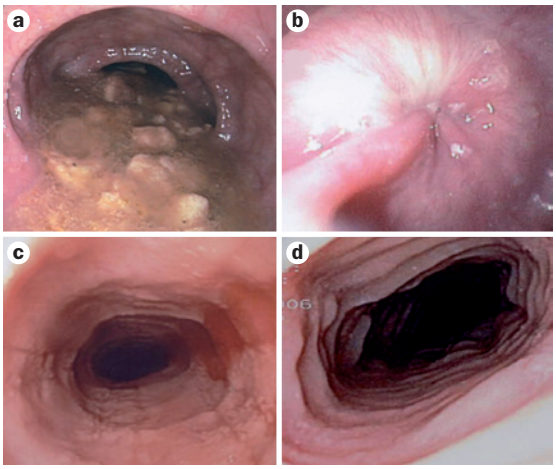

Figure 1 | Endoscopic features of dysphagia. Features of oesophageal achalasia **a** | oesophageal stasis and **b** | 'tight' EGJ. Features of eosinophilic oesophagitis **c** | longitudinal furrows and **d** | concentric rings. Abbreviation: EGJ, oesophagogastric junction.

Oesophageal manometry

Methodologies for performing diagnostic pressure measurements within the gut have evolved considerably during the last 20 years. Advances in catheter technology now offer improved reliability, recording fidelity and spatial resolution of measurements. Catheter diameter has also reduced, enabling motility investigations in children to become routine. Oesophageal manometry is a short, well-tolerated procedure, which can be very useful for diagnosing the presence of a primary oesophageal motor disorder that might explain dysphagia symptoms. Manometry testing utilizes an indwelling catheter to measure the pressures generated during transport of a swallowed bolus from pharynx to stomach. This approach provides an objective measurement of the resting and relaxation pressures of the oesophageal sphincters and the pressures generated by oesophageal peristaltic contraction. Intrabolus pressures within the lumen of the distal oesophagus can also be measured. High-resolution manometry (HRM) is the current state-of-the-art for this measurement method and typically involves recording of intraluminal pressure using a large array of closely spaced pressure sensors (typically 32–36 sensors at 1 cm spacing). High-resolution pressures are displayed over time by way of spatiotemporal pressure plots (also called oesophageal pressure topography [EPT] or Clouse plots). EPT plots can be quantitatively evaluated for diagnosis through the derivation of EPT metrics, of which five are currently in routine use (Figure 2). Derivation of EPT metrics has been made both objective and reliable using interactive software. Interpretation of the EPT results is then guided through application of the Chicago classification diagnostic algorithm.[20] HRM can reveal residual pressure at the crural diaphragm or elevated intrabolus pressure proximal to the EGJ.[21] Hiatus hernia might cause an EGJ outflow obstruction, particularly in patients with dysphagia, but without typical GERD symptoms. Three EGJ pressure morphology subtypes have been defined, which are primarily distinguished by the extent of separation between the crural diaphragm and the lower oesophageal sphincter.[22]

Current diagnostic criteria used by the Chicago classification algorithm are based on a standardized protocol of 10 × 5 ml liquid bolus swallows performed in a supine posture.[19] However, in our experience, most patients who develop dysphagia owing to a primary motor disorder experience symptoms in relation to solids rather than liquids and, indeed, often report no symptoms during performance of a manometric test. EPT metrics also do not seem to correlate with the intensity of bolus perception experience during the test.[23] Considerable debate has surrounded the issue of the potential added value of testing using a more physiological posture (that is, upright) and with solid bolus challenges or a meal in order to precipitate symptoms and to characterize the adaptive response of the oesophagus to an increased work load; notably, this adaptive response has been shown to be diminished in patients with erosive GERD.[24] Data from studies assessing the normative range in the upright posture and with solid bolus challenges for EPT metrics are emerging and could potentially lead to expansion of the range of swallow protocols upon which a diagnosis using the Chicago classification algorithm can be based.[25]

In the paediatric setting, the spectrum of motility disorders that can be classified by HRM resembles that seen in adults.[26] However, implementation of HRM for use in the paediatric population is challenging owing to the lack of data on paediatric normative ranges for EPT metrics. The age and size of the patient also affects some HRM metrics[26,27] and paediatric studies are more challenging to perform, meaning that studies often have fewer than the requisite 10 liquid swallows and the scope for provocative testing is limited. Multiple swallowing, movement and crying can also produce pressure artefacts.

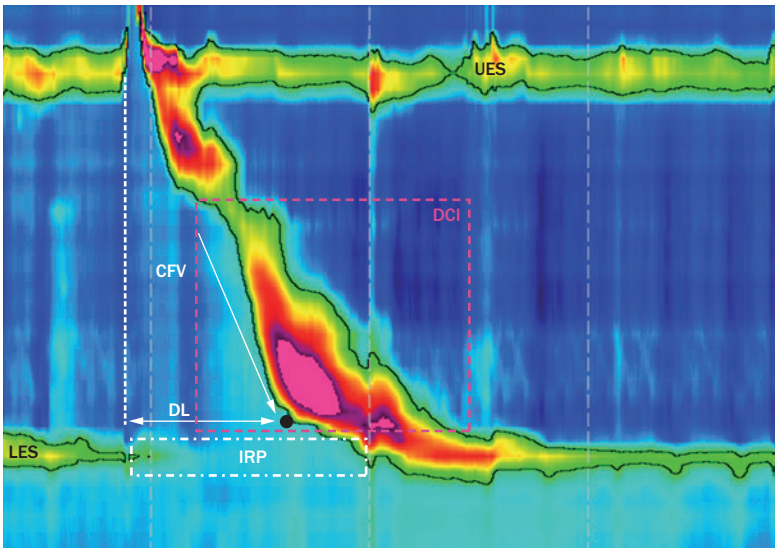

Figure 2 | Oesophageal pressure topography Clouse plots of a normal water swallow on high-resolution manometry. The two bands of high pressure correspond to the UES and LES. The IRP is the lowest average pressure for four noncontiguous seconds, defining LES relaxation. The UES relaxes at the start of the swallow, and the LES relaxes as the contraction front traverses the oesophageal body. The CDP (black dot) is the inflexion point in the contractile front propagation. The CFV corresponds to the slope of the tangent line to the initial portion of the contraction. The distal latency is measured from the onset of swallow (dashed vertical line) to the CDP. The DCI corresponds to the volume of the contraction between the first pressure trough and the distal trough. Abbreviations: CDP, contractile deceleration point; CFV, contractile front velocity; DCI, distal contractile integral; DL, distal latency; IRP, integrated relaxation pressure; LES, lower oesophageal sphincter; UES, upper oesophageal sphincter.

Intraluminal impedance

Manometry results can be inconclusive or even normal despite a clinical history suggesting an underlying oesophageal motility disorder.[23] Such findings might dictate the need for further corroborative evidence of abnormal bolus transport, such as from fluoroscopy (as mentioned previously) or intraluminal impedance measurement. The measurement of electrical impedance along a catheter by way of an electrode array is now a standard add-on feature of oesophageal manometry systems. Impedance measurements detect movement and clearance of a conductive bolus. Although this approach provides physiological insights, the additional yield of measuring impedance in relation to understanding pathophysiology is limited. The analysis of impedance recordings remains fairly simplistic and does not go beyond the detection of bolus transport failure, which is already highly predictable with the use of HRM results.[28,29] New and different ways of analysing impedance waveforms through integration with pressure measurement are now being explored, with studies suggesting that impedance can be used to track subtle variations in bolus movement,[30] quantify luminal diameter changes[31–33] and time the period of bolus flow across the EGJ.[34] Further research is needed to determine whether these additional insights have clinical utility.

Intrabolus pressure captured during HRM is generally considered to be a definitive correlate of increased flow resistance as measured by manometry; however, such pressures are often difficult to measure and tend to be ignored unless unequivocally elevated. The measurement of intraluminal impedance could help guide intrabolus pressure measurements as it has been confirmed that the lowest level of impedance (nadir impedance) defines maximum bolus distension in space and time.[32] Hence, the pressures measured at nadir impedance define intrabolus distension and emptying pressures during bolus transport.[30,35] Such pressures in and around the bolus being transported might have physiological and pathophysiological relevance and seem to correlate with symptoms.[35,36] Finally, impedance measurements might give the potential to assess oesophageal passive drainage in patients with achalasia.[37,38] When combined with pressure measurements of the EGJ, impedance measurements could provide a broader scope of mechanistic information than that currently available using a timed barium oesophagram test and have a greater role in the diagnosis of dysphagia than originally envisaged.

Impedance planimetry

Some aspects of oesophageal function are not readily appreciable using HRM techniques alone. Most evident are the mechanical properties of the gut wall, which alter oesophageal compliance and therefore bolus flow-resistance along the oesophageal body and through the upper and lower oesophageal sphincters. Oesophageal compliance can reduce in concert with a disease process, which leads to loss of neuromechanical function (for example, achalasia) and tissue remodelling (eosinophilic oesophagitis). Repeated therapy such as dilation can also lead to fibrosis and subsequent complications. The technique of impedance planimetry, by way of a functional luminal imaging probe (FLIP), could provide compliance information. Comprising of a compliant bag, an array of impedance electrodes and a pressure sensor, the FLIP can quantify the distensibility of surrounding structures based on the relationship between bag cross-sectional area and intra-bag pressure and/or volume. FLIP has already been applied in two key areas and could have great diagnostic relevance. First, FLIP has been used to predict treatment success by assessing EGJ distensibility, particularly in relation to achalasia.[39] Second, FLIP has been used to predict bolus impaction risk by assessment of oesophageal distensibility in relation to eosinophilic oesophagitis (Figure 3).[40]

Although an important determinant of treatment strategies, distinguishing patients with hypersensitivity from those with true motor dysfunctions is not always straightforward, even when state-of-the-art HRM is used. Oesophageal perception can be evoked by graded distensions applied using the impedance planimetry balloon, thus enabling the direct correlation of wall tension and sensory thresholds. Patients with hypersensitivity (for example patients with noncardiac chest pain) demonstrate lower tension thresholds to elicit sensation than patients with true motor dysfunctions.[41] Impedance planimetry of the oesophagus could also have a role in detecting subtle mechanical dysfunction that might explain symptoms of dysphagia.[42]

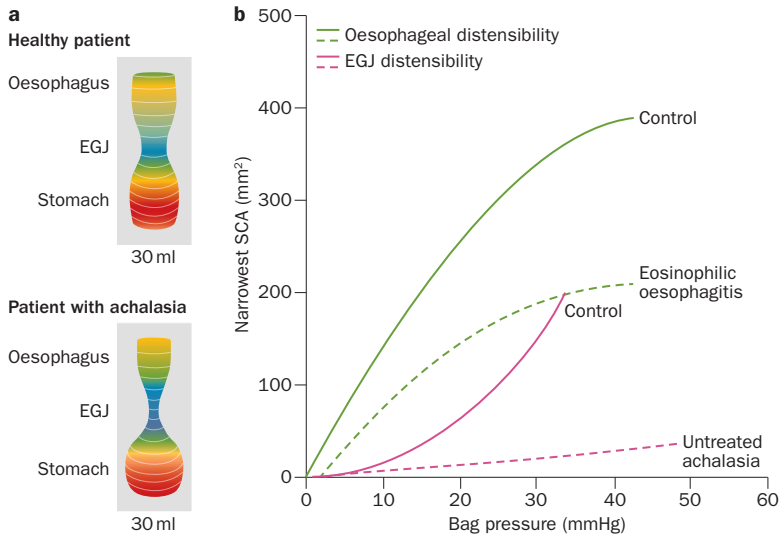

Figure 3 | Impedance planimetry to assess distensibility of the oesophagus and EGJ. **a** | FLIP measurement panels showing the diameter profile across the EGJ in a healthy person and a patient with achalasia. **b** | Distensibility curves for the distal oesophagus, in controls and patients with eosinophilic oesophagitis and for the EGJ in control individuals and patients with untreated achalasia. This figure was constructed based on published findings. Abbreviations: EGJ, oesophagogastric junction; FLIP, functional luminal imaging probe. Permission obtained from Elsevier Ltd. © Rohof, W. O. *et al. Gastroenterology* **143**, 328–335 (2012)[39] and Nicodeme, F. *et al. Clin. Gastroenterol. Hepatol.* **11**, 1101–1107 (2013).[40]

Diagnosis of oesophageal dysphagia

GERD-related dysphagia

Dysphagia is a common symptom of GERD and might be related to oesophagitis, peptic stricture, oesophageal carcinoma or GERD-related oesophageal motility disorders.[43] Erosive oesophagitis, which develops in patients with chronic GERD, is defined by the presence of mucosal breaks in the oesophageal mucosa at the EGJ and is best classified according to the Los Angeles classification.[44] Reflux oesophagitis is present in 10–30% of patients with reflux symptoms and approximately one-third of patients with oesophagitis report non-troublesome dysphagia that resolves with PPI therapy.[45] According to the Montreal definition, "troublesome dysphagia is present when patients need to alter eating patterns or report food impaction"[43] and is considered as an alarm symptom indicative of serious oesophageal pathology such as peptic stricture or oesophageal cancer that warrants further investigation. Indeed, GERD symptoms are not singularly associated with oesophageal carcinoma;[46] having dysphagia has been reported to increase the likelihood of having oesophageal cancer.[47] The prevalence of oesophageal strictures is low (<5% in population-based studies) and has declined as PPI therapy has become widespread.[48] GERD-associated motility disorders such as hypotensive or failed peristalsis usually increase in parallel with reflux severity and might be responsible for nonobstructive dysphagia in patients with GERD.[49]

Dysphagia is also a common symptom in patients who undergo antireflux surgery (for example, Nissen fundoplication). Many patients experience dysphagia of a transient nature during the immediate postoperative period. However, persistent and troublesome dysphagia is less common, affecting 8–12% of patients in randomized controlled trials, and leads to dilation and/or surgical re-intervention in up to 7% of patients.[50,51] A meta-analysis of randomized controlled trials showed that the prevalence of postoperative dysphagia was lower (8.6%) after laparoscopic anterior (180°) fundoplication than after 'full wrap' laparoscopic Nissen (360°) fundoplication (13.5%), with a similar effect on control of reflux symptoms.[50] Whether the occurrence of postoperative dysphagia can be predicted by oesophageal motility testing performed preoperatively remains a matter of debate. However, some encouraging data suggest that subtle, subclinical dysfunctions of motility, detectable by combined pressure-impedance analysis[52,53] and/or multiple rapid swallow testing,[54] could predict susceptibility to postoperative dysphagia. Although these data are preliminary, they suggest the potential for an individual patient's risk for dysphagia to be better quantified than is currently possible. Such a change might enable improved determination of risks versus benefits of surgery and/or decision making with respect to optimal operative approach.

Eosinophilic oesophagitis

Over the past 15 years, eosinophilic oesophagitis has become recognized as one of the most prevalent causes of oesophageal dysphagia in adults,[55] probably because of an increased awareness of both endoscopists and pathologists.[56] Eosinophilic oesophagitis is an allergic disorder defined by symptoms related to oesophageal dysfunction and characterized by an eosinophil-predominant inflammation on analysis of oesophageal biopsy samples.[7] Mucosal eosinophilia is usually isolated to the oesophagus, characteristically consisting of a peak value of ≥15 eosinophils per high-power field. Other causes of oesophageal eosinophilia such as vasculitis, eosinophilic gastroenteritis, hypereosinophilic syndrome, acute infections, Crohn's disease or connective tissue diseases should be excluded. The pathogenesis of eosinophilic oesophagitis involves genetic susceptibility[57] and dysregulated immunity directed at food antigens as demonstrated by the efficacy of elementary or elimination diets in improving symptoms.[58,59] GERD and eosinophilic oesophagitis might be related diseases as up to 50% of patients with an eosinophilic oesophagitis phenotype respond to PPI therapy both clinically and histologically,[60] leading to the concept of 'PPI-responsive oesophageal eosinophilia'. A 2014 study has shown that oesophageal permeability was increased in both eosinophilic oesophagitis and PPI-responsive oesophageal eosinophilia, which enabled transepithelial transport of food antigens.[61] PPI therapy can at least partially restore mucosal integrity in PPI-responsive oesophageal eosinophilia but not in eosinophilic oesophagitis.[61] Dysphagia can be related to oesophageal stricture, observed in approximately one-third of patients with eosinophilic oesophagitis,[13] or to oesophageal motility disorders secondary to oesophageal mucosal infiltration of the oesophageal wall. However, as most patients

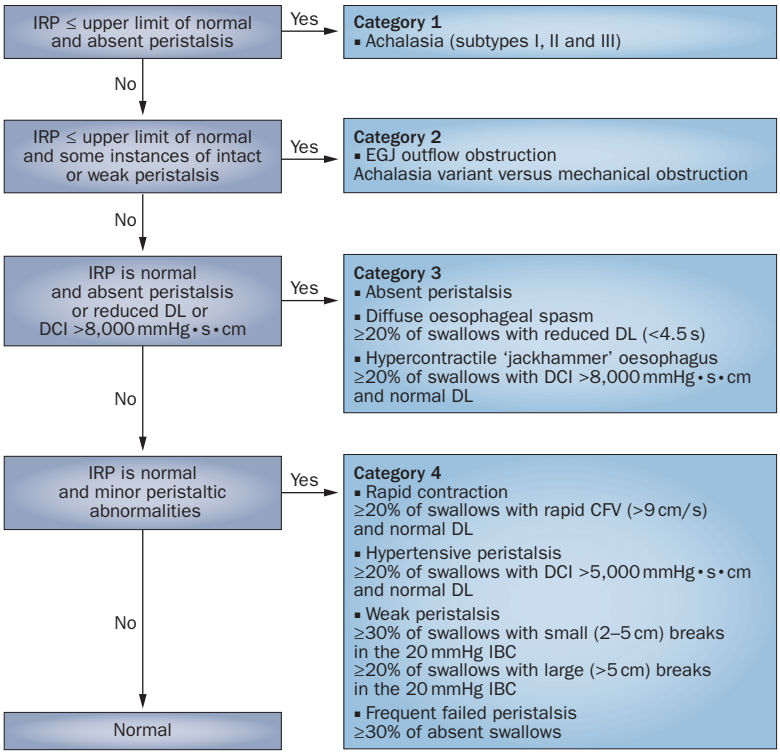

Figure 4 | Flow diagram illustrating the hierarchical analysis of patient EPT findings according to the Chicago classification.[20] Abbreviations: CFV, contractile front velocity; DCI, distal contractile integral; DL, distal latency; EGJ, oesophagogastric junction; EPT: oesphageal pressure topography; IBC, isobaric contour; IRP, integrated relaxation pressure.

with eosinophilic oesophagitis have normal oesophageal motility,[62] decreased oesophageal distensibility has been suggested to cause dysphagia.[63]

Eosinophilic oesophagitis is most frequently observed in young adult males, during the third or fourth decade of life[64] and is frequently (>75%) associated with other allergic disorders such as asthma, atopic rhinitis or eczema.[65] Dysphagia is the most frequent symptom in adults with eosinophilic oesophagitis; other symptoms include chest pain, heartburn and abdominal pain.[65] Food impaction requiring endoscopic bolus removal frequently leads to diagnosis and occurs in 30–50% of patients.[66] In children, dysphagia is less prevalent than in adults with pain, vomiting or feeding difficulties being the most frequent clinical manifestations. As outlined above, the most frequently observed endoscopic features of eosinophilic oesophagitis are rings, furrows, exsudates and strictures (Figure 2) but normal endoscopic appearance can be observed in up to 25% of patients (adults and children) with eosinophilic oesophagitis, thus justifying the need to obtain oesophageal biopsy samples in all patients with unexplained dysphagia.[13] For accurate diagnosis, at least four biopsy samples from two different locations (that is in the distal and proximal oesophagus) should be taken.[7]

Primary oesophageal motor disorders

Oesophageal manometry can reveal manometric features of bolus swallowing such as the oesophageal peristaltic wave, transition zone, and relaxation and movement of the EGJ. HRM can also evaluate pharyngeal (tongue base pressure) and upper oesophageal sphincter relaxation during swallowing. To date, the major focus of HRM studies for the investigation of oesophageal dysphagia has been the identification of disordered peristalsis and/or high EGJ pressures. Pharyngeal propulsion also helps facilitate bolus transport so that the more effective the swallowing force, the less work the oesophagus will need to do to finalize transport of the bolus into the stomach.[30]

The present Chicago classification algorithm is highly useful to the clinician because it provides a unified HRM and consensus-based framework enabling recognition of specific oesophageal dysfunctions.[19] These dysfunctions might cause failure of transport along the oesophagus (for example weak propulsion), pain symptoms (such as hypercontractility or spasticity) or impede bolus flow through the EGJ (obstruction). The evolving Chicago classification algorithm is the current best-practice for manometric diagnosis of oesophageal motor disorders and characterizes oesophageal motor dysfunction into four main categories in order of severity: achalasia (Category 1); EGJ outflow obstruction (Category 2); disorders never observed in healthy individuals such as absent peristalsis, diffuse oesophageal spasm or hypercontractile oesophagus (Category 3); and motor patterns outside the normal range, for example weak peristalsis, frequent failed peristalsis, hypertensive peristalsis or rapid contraction (Category 4, Figure 4). To arrive at a specific Chicago classification diagnosis, five different EPT metrics are calculated for each swallow (Figure 2): first, the 4 s integrated relaxation pressure (which defines EGJ relaxation pressures); second, the largest size of breaks in the peristaltic contractile front (break size; which defines peristaltic integrity over distance based on the 20 mmHg isocontour); third, the velocity of the contractile front (which defines peristaltic contraction rate); fourth, the integral of pressure generated by contraction of the distal oesophagus (which defines strength or weakness of contractility); and fifth, the time latency from swallow onset to the contractile deceleration point (which signifies the time of transition of oesophageal emptying into the stomach). Distal latency is the latest metric to be added to the Chicago classification and is thought to describe contractions of abnormally early onset and rapid onset better than the contractile front velocity. The physiological and pathological basis underpinning the utility of the five metrics is well supported by published evidence.[20,67,68]

As previously mentioned, defining 'normal' oesophageal motility is just as important as determining a motor disorder. A normal manometry study could identify a patient whose symptoms might be caused by visceral hypersensitivity (see section on functional dysphagia). A reliable measurement of EGJ pressures is also critical because the diagnostic algorithm purposefully emphasizes the identification of EGJ dysfunction as a key diagnostic parameter to confirm or exclude achalasia. Among the various diagnostic categories, Category 1 disorders

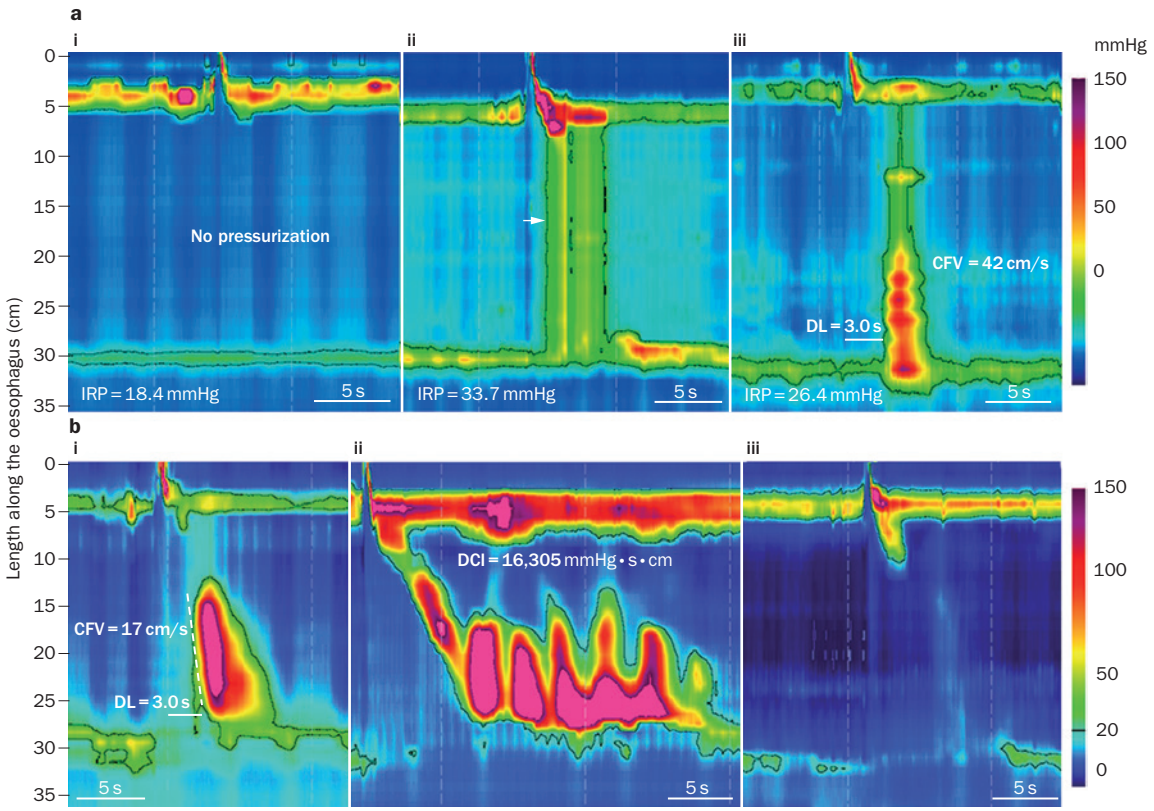

Figure 5 | Examples of major oesophageal motility disorders never seen in healthy individuals. **a** | The three achalasia subtypes, (i) type I no compression (ii) type II with compression (arrow) (iii) type III (spastic achalasia). **b** | Examples of non-achalasic major motor disorders. (i) oesophageal spasm (premature contraction, short distal latency) (ii) hypercontractile 'jackhammer' oesophagus (DCI >8,000 mmHg.s.cm (iii) absent peristalsis. Abbreviations: CFV, contractile front velocity; DCI, distal contractile integral; DL, distal latency; IRP, integrated relaxation pressure.

(achalasia subtypes) are considered most important.[19] HRM criteria can be used to distinguish three predominant achalasia subtypes (Figure 5), namely classic (type I) achalasia without compression, type II (achalasia) with compression and type III (spastic achalasia).[69,70] Importantly, achalasia subtyping in this way seems to be predictive of response to interventions designed to ablate flow resistance at the EGJ.[70]

If an achalasia subtype is not seen then a Category 2 disorder, such as EGJ outflow obstruction, needs to be excluded. Category 2 disorders include a subgroup of patients with some preserved peristalsis and typically distal compartmentalized pressurization, which is a marker of abnormal pressurization of the bolus 'sandwiched' between the advancing contractile front and the EGJ. This subgroup of patients has been suggested to represent an achalasia variant or early manifestation of achalasia.[69]

Beyond the achalasia subtypes and variants the clinical significance of abnormal Chicago classification findings might be less clear. The mechanisms that generate EGJ pressure are complex and the 4 s integrated relaxation pressure measurement reflects the composite effects of pressure generated by both the intrinsic lower oesophageal sphincter and the extrinsic crural diaphragm sphincter.[19] Importantly, the complexity of pressure generation can produce erroneous high pressure recordings.[71] Hence, patients meeting criteria for EGJ outflow obstruction, but who do not demonstrate evidence of distal compartmentalized pressurization (or other evidence of interrupted trans-EGJ flow) might not have obstruction even though they have been classified as such. Finally, in the case of patients with Category 3 and 4 disorders, corroboratory evidence of symptom association with motor patterns (for example, chest pain with spasm or hypercontractility of the oesophagus) or corroborative abnormalities (such as symptoms of hold-up or evidence of extreme bolus retention with frequent failed peristalsis) might be needed to classify them as being clinically meaningful. Motor patterns in Category 4, such as weak peristalsis with large breaks and bolus retention, are seen in control cohorts,[72] therefore, the clinical significance of these patterns in isolation is unclear.

Functional dysphagia

According to the Rome III classification, functional dysphagia is defined by "a sensation of abnormal bolus transit through the oesophageal body after exclusion of structural lesions, GERD and histopathology-based oesophageal motor disorders".[3] The definition requires exclusion of organic stricture, eosinophilic oesophagitis and well-characterized primary oesophageal motility disorders by appropriate investigations such as

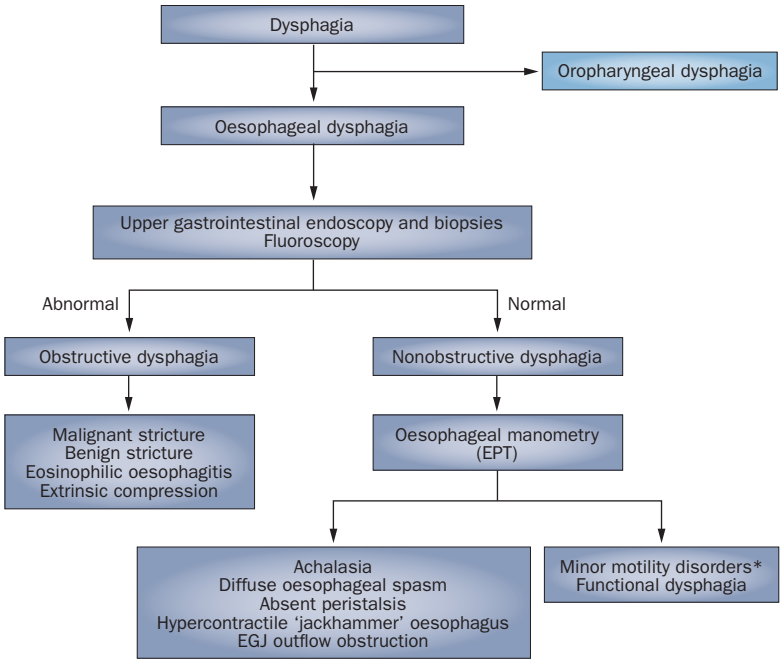

Figure 6 | Diagnosis algorithm for oesophageal dysphagia. *Minor motor disorders are rapid contractions, weak peristalsis, frequent failed peristalsis and hypertensive 'nutcracker' oesophagus. Abbreviations: EGJ, oesophagogastric junction; EPT, oesophageal pressure topography.

endoscopy and biopsy, barium swallow and oesophageal manometry (HRM with oesophageal pressure topography). Some degree of oesophageal dysmotility, combined with increased intraoesophageal sensory perception, could be involved in the pathogenesis of functional dysphagia.[3] However, if a primary motor disorder, such as achalasia, EGJ outflow obstruction, diffuse oesophageal spasm, absent peristalsis or hypercontractile 'jackhammer' oesophagus, is seen then this finding would be inconsistent with functional dysphagia. As the clinical significance of minor oesophageal motor abnormalities such as weak peristalsis (peristaltic breaks), frequent failed peristalsis, rapid contractions and hypertensive 'nutcracker' oesophagus is less clear, then these so-called abnormalities might not necessarily exclude functional dysphagia.[19] Provocative measures such as multiple rapid swallows or solid swallows could reveal a motor dysfunction missed using the standard 10 × 5 ml liquid protocol. Solid swallows or ingestion of a standardized meal during manometry might demonstrate a link between the onset of bolus hold-up symptoms and failure of the oesophageal body to physiologically compensate for an increasing workload for effective bolus transport. Such findings would again be consistent with a primary motor disorder and not functional dysphagia.[25,73] Similarly, in patients with dysphagia who have oesophageal motility determined to be 'normal' on manometric criteria, sophisticated investigations that combine and integrate oesophageal pressure and impedance recordings seem to reveal subtle pressure-flow and mechanical abnormalities, which could explain symptoms.[35,36,74,75] Impedance planimetry[42] might also improve detection of subtle abnormalities. Although subtle, such findings arguably suggest a neuromechanical dysfunction and not necessarily functional dysphagia.

Conclusion

Oesophageal dysphagia is a common symptom that encompasses a wide spectrum of aetiologies, from neoplasia to functional disorders. A thorough patient history and endoscopy with oesophageal biopsies are the two most important first steps for diagnosis (Figure 6). Fluoroscopy might be useful to evaluate rings, webs and hiatal hernia. Once obstructive dysphagia has been ruled out, oesophageal manometry is the key investigation, best performed with HRM to characterize oesophageal motility. Major oesophageal motor disorders detected can be defined according to the Chicago classification. The clinical relevance of other motility disorders remains questionable. Whether more sophisticated investigations than the ones currently in use will improve detection of subtle abnormalities in bolus transport and perception and thus help to identify a subgroup of patients with functional dysphagia needs to be determined.

Review criteria

For the purpose of this Review, articles were selected in PubMed database among full-text papers published in the past 15 years in English that were identified using the search terms "dysphagia", "functional dysphagia", "eosinophilic oesophagitis", "oesophageal motor disorders" and "achalasia".

1. Eslick, G. D. & Talley, N. J. Dysphagia: epidemiology, risk factors and impact on quality of life—a population-based study. *Aliment. Pharmacol. Ther.* **27**, 971–979 (2008).
2. Lindgren, S. & Janzon, L. Prevalence of swallowing complaints and clinical findings among 50–79 year-old men and women in an urban population. *Dysphagia* **6**, 187–192 (1991).
3. Galmiche, J. P. *et al.* Functional esophageal disorders. *Gastroenterology* **130**, 1459–1465 (2006).
4. Roeder, B. E., Murray, J. A. & Dierkhising, R. A. Patient localization of esophageal dysphagia. *Dig. Dis. Sci.* **49**, 697–701 (2004).
5. Chen, C. L. & Orr, W. C. Comparison of esophageal motility in patients with solid dysphagia and mixed dysphagia. *Dysphagia* **20**, 261–265 (2005).
6. Zografos, G. N., Georgiadou, D., Thomas, D., Kaltsas, G. & Digalakis, M. Drug-induced esophagitis. *Dis. Esophagus* **22**, 633–637 (2009).
7. Dellon, E. S. *et al.* ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am. J. Gastroenterol.* **108**, 679–692 (2013).
8. Belafsky, P. C. *et al.* Validity and reliability of the eating assessment tool (EAT-10). *Ann. Otol. Rhinol. Laryngol.* **117**, 919–924 (2008).
9. McElhiney, J. *et al.* The mayo dysphagia questionnaire-30: documentation of reliability and validity of a tool for interventional trials in adults with esophageal disease. *Dysphagia* **25**, 221–230 (2010).
10. Rommel, N., De Meyer, A. M., Feenstra, L. & Veereman-Wauters, G. The complexity of feeding problems in 700 infants and young children presenting to a tertiary care institution. *J. Pediatr. Gastroenterol. Nutr.* **37**, 75–84 (2003).
11. Singendonk, M. M., Rommel, N., Omari, T. I., Benninga, M. A. & van Wijk, M. P. Upper gastrointestinal motility: prenatal development and problems in infancy. *Nat. Rev. Gastroenterol. Hepatol.* **11**, 545–555 (2014).
12. Muller, M. *et al.* Is the Schatzki ring a unique esophageal entity? *World J. Gastroenterol.* **17**, 2838–2843 (2011).

13. Hirano, I. *et al.* Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. *Gut* **62**, 489–495 (2013).
14. Muller, S., Puhl, S., Vieth, M. & Stolte, M. Analysis of symptoms and endoscopic findings in 117 patients with histological diagnoses of eosinophilic esophagitis. *Endoscopy* **39**, 339–344 (2007).
15. Ponsot, P. *et al.* Chronic esophagitis dissecans: an unrecognized clinicopathologic entity? *Gastrointest. Endosc.* **45**, 38–45 (1997).
16. Hokama, A. *et al.* Esophagitis dissecans superficialis and autoimmune bullous dermatoses: A review. *World J. Gastrointest. Endosc.* **2**, 252–256 (2010).
17. Katzka, D. A. *et al.* Variations in presentations of esophageal involvement in lichen planus. *Clin. Gastroenterol. Hepatol.* **8**, 777–782 (2010).
18. Vaezi, M. F., Baker, M. E., Achkar, E. & Richter, J. E. Timed barium oesophagram: better predictor of long term success after pneumatic dilation in achalasia than symptom assessment. *Gut* **50**, 765–770 (2002).
19. Vaezi, M. F., Baker, M. E. & Richter, J. E. Assessment of esophageal emptying post-pneumatic dilation: use of the timed barium esophagram. *Am. J. Gastroenterol.* **94**, 1802–1807 (1999).
20. Bredenoord, A. J. *et al.* Chicago classification criteria of esophageal motility disorders defined in high resolution esophageal pressure topography. *Neurogastroenterol. Motil.* **24** (Suppl. 1), 57–65 (2012).
21. Pandolfino, J. E., Kwiatek, M. A., Ho, K., Scherer, J. R. & Kahrilas, P. J. Unique features of esophagogastric junction pressure topography in hiatus hernia patients with dysphagia. *Surgery* **147**, 57–64 (2010).
22. Kahrilas, P. J. & Peters, J. H. Evaluation of the esophagogastric junction using high resolution manometry and esophageal pressure topography. *Neurogastroenterol. Motil.* **24** (Suppl. 1), 11–19 (2012).
23. Xiao, Y. *et al.* Lack of correlation between HRM metrics and symptoms during the manometric protocol. *Am. J. Gastroenterol.* **109**, 521–526 (2014).
24. Daum, C. *et al.* Failure to respond to physiologic challenge characterizes esophageal motility in erosive gastro-esophageal reflux disease. *Neurogastroenterol. Motil.* **23**, 517–e200 (2011).
25. Sweis, R. *et al.* Normative values and inter-observer agreement for liquid and solid bolus swallows in upright and supine positions as assessed by esophageal high-resolution manometry. *Neurogastroenterol. Motil.* **23**, 509–e198 (2011).
26. Singendonk, M. M. J. *et al.* Applying the Chicago Classification criteria of esophageal motility to a pediatric cohort: effects of patient age and size. *Neurogastroenterol. Motil.* **26**, 1333–1341 (2014).
27. Chumpitazi, B. & Nurko, S. Pediatric gastrointestinal motility disorders: challenges and a clinical update. *Gastroenterol. Hepatol. (N.Y.)* **4**, 140–148 (2008).
28. Fox, M. *et al.* High-resolution manometry predicts the success of oesophageal bolus transport and identifies clinically important abnormalities not detected by conventional manometry. *Neurogastroenterol. Motil.* **16**, 533–542 (2004).
29. Omari, T., Tack, J. & Rommel, N. Impedance as an adjunct to manometric testing: What it has failed to do and what it may tell us in the future. *United European Gastroenterol. J.* **2**, 355–366 (2014).
30. Omari, T., Kritas, S. & Cock, C. New insights into pharyngo-esophageal bolus transport revealed by pressure-impedance measurement. *Neurogastroenterol. Motil.* **24**, 549–556 (2012).
31. Imam, H., Marrero, F. & Shay, S. Impedance nadir values correlate with barium bolus amount. *Dis. Esophagus* **25**, 600–607 (2012).
32. Kim, J. H., Mittal, R. K., Patel, N., Ledgerwood, M. & Bhargava, V. Esophageal distension during bolus transport: can it be detected by intraluminal impedance recordings? *Neurogastroenterol. Motil.* **26**, 1122–1130 (2014).
33. Omari, T. I. *et al.* Upper esophageal sphincter impedance as a marker of sphincter opening diameter. *Am. J. Physiol. Gastrointest. Liver Physiol.* **302**, 909–913 (2012).
34. Lin, Z. *et al.* Flow time through esophagogastric junction derived during high-resolution impedance-manometry studies: a novel parameter for assessing esophageal bolus transit. *Am. J. Physiol. Gastrointest. Liver Physiol.* **307**, 158–163 (2014).
35. Omari, T. I., Wauters, L., Rommel, N., Kritas, S. & Myers, J. C. Oesophageal pressure-flow metrics in relation to bolus volume, bolus consistency, and bolus perception. *United European Gastroenterol. J.* **1**, 249–258 (2013).
36. Chen, C. L., Yi, C. H., Liu, T. T., Hsu, C. S. & Omari, T. I. Characterization of esophageal pressure-flow abnormalities in patients with non-obstructive dysphagia and normal manometry findings. *J. Gastroenterol. Hepatol.* **28**, 946–953 (2013).
37. Cho, Y. K. *et al.* Assessing bolus retention in achalasia using high-resolution manometry with impedance: a comparator study with timed barium esophagram. *Am. J. Gastroenterol.* **109**, 829–835 (2014).
38. Conchillo, J. M., Selimah, M., Bredenoord, A. J., Samsom, M. & Smout, A. J. Assessment of oesophageal emptying in achalasia patients by intraluminal impedance monitoring. *Neurogastroenterol. Motil.* **18**, 971–977 (2006).
39. Rohof, W. O., Hirsch, D. P., Kessing, B. F. & Boeckxstaens, G. E. Efficacy of treatment for patients with achalasia depends on the distensibility of the esophagogastric junction. *Gastroenterology* **143**, 328–335 (2012).
40. Nicodeme, F. *et al.* Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. *Clin. Gastroenterol. Hepatol.* **11**, 1101–1107 (2013).
41. Gregersen, H., Kwiatek, M. A., Schwizer, W. & Tutuian, R. Contribution of sensitivity, volume and tone to visceral perception in the upper gastrointestinal tract in man: emphasis on testing. *Neurogastroenterol. Motil.* **19**, 47–61 (2007).
42. Lin, Z. *et al.* Regional variation in distal esophagus distensibility assessed using the functional luminal imaging probe (FLIP). *Neurogastroenterol. Motil.* **25**, 765–771 (2013).
43. Vakil, N., van Zanten, S. V., Kahrilas, P., Dent, J. & Jones, R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am. J. Gastroenterol.* **101**, 1900–1920 (2006).
44. Armstrong, D. *et al.* The endoscopic assessment of esophagitis: a progress report on observer agreement. *Gastroenterology* **111**, 85–92 (1996).
45. Vakil, N. B., Traxler, B. & Levine, D. Dysphagia in patients with erosive esophagitis: prevalence, severity, and response to proton pump inhibitor treatment. *Clin. Gastroenterol. Hepatol.* **2**, 665–668 (2004).
46. Rubenstein, J. H. & Taylor, J. B. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. *Aliment. Pharmacol. Ther.* **32**, 1222–1227 (2010).
47. Fransen, G. A., Janssen, M. J., Muris, J. W., Laheij, R. J. & Jansen, J. B. Meta-analysis: the diagnostic value of alarm symptoms for upper gastrointestinal malignancy. *Aliment. Pharmacol. Ther.* **20**, 1045–1052 (2004).
48. El-Serag, H. B. & Lau, M. Temporal trends in new and recurrent oesophageal strictures in a Medicare population. *Aliment. Pharmacol. Ther.* **25**, 1223–1229 (2007).
49. Savarino, E. *et al.* Oesophageal motility and bolus transit abnormalities increase in parallel with the severity of gastro-oesophageal reflux disease. *Aliment. Pharmacol. Ther.* **34**, 476–486 (2011).
50. Broeders, J. A. *et al.* Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. *Br. J. Surg.* **97**, 1318–1330 (2010).
51. Galmiche, J. P. *et al.* Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. *JAMA* **305**, 1969–1977 (2011).
52. Loots, C. *et al.* Gastroesophageal reflux, esophageal function, gastric emptying, and the relationship to dysphagia before and after antireflux surgery in children. *J. Pediatr.* **162**, 566–573 (2013).
53. Myers, J. C. *et al.* Susceptibility to dysphagia after fundoplication revealed by novel automated impedance manometry analysis. *Neurogastroenterol. Motil.* **24**, 812–e393 (2012).
54. Stoikes, N. *et al.* The value of multiple rapid swallows during preoperative esophageal manometry before laparoscopic antireflux surgery. *Surg. Endosc.* **26**, 3401–3407 (2012).
55. Kidambi, T., Toto, E., Ho, N., Taft, T. & Hirano, I. Temporal trends in the relative prevalence of dysphagia etiologies from 1999–2009. *World J. Gastroenterol.* **18**, 4335–4341 (2012).
56. Syed, A. A. *et al.* The rising incidence of eosinophilic oesophagitis is associated with increasing biopsy rates: a population-based study. *Aliment. Pharmacol. Ther.* **36**, 950–958 (2012).
57. Rothenberg, M. E. *et al.* Common variants at 5q22 associate with pediatric eosinophilic esophagitis. *Nat. Genet.* **42**, 289–291 (2010).
58. Gonsalves, N. *et al.* Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology* **142**, 1451–1459 (2012).
59. Lucendo, A. J. *et al.* Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J. Allergy Clin. Immunol.* **131**, 797–804 (2013).
60. Molina-Infante, J. *et al.* Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin. Gastroenterol. Hepatol.* **9**, 110–117 (2011).
61. van Rhijn, B. D. *et al.* Proton pump inhibitors partially restore mucosal integrity in patients with proton pump inhibitor-responsive esophageal eosinophilia but not eosinophilic esophagitis. *Clin. Gastroenterol. Hepatol.* **12**, 1815–1823 (2014).
62. Roman, S. *et al.* Manometric features of eosinophilic esophagitis in esophageal pressure topography. *Neurogastroenterol. Motil.* **23**, 208–214 (2011).

63. Kwiatek, M. A. *et al.* Mechanical properties of the esophagus in eosinophilic esophagitis. *Gastroenterology* **140**, 82–90 (2011).
64. van Rhijn, B. D., Verheij, J., Smout, A. J. & Bredenoord, A. J. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. *Neurogastroenterol. Motil.* **25**, 47–52 (2013).
65. Furuta, G. T. *et al.* Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* **133**, 1342–1363 (2007).
66. Desai, T. K. *et al.* Association of eosinophilic inflammation with esophageal food impaction in adults. *Gastrointest. Endosc.* **61**, 795–801 (2005).
67. Carlson, D. A. & Pandolfino, J. E. The Chicago criteria for esophageal motility disorders: what has changed in the past 5 years? *Curr. Opin. Gastroenterol.* **28**, 395–402 (2012).
68. Kahrilas, P. J. Esophageal motor disorders in terms of high-resolution esophageal pressure topography: what has changed? *Am. J. Gastroenterol.* **105**, 981–987 (2010).
69. Kahrilas, P. J. & Boeckxstaens, G. The spectrum of achalasia: lessons from studies of pathophysiology and high-resolution manometry. *Gastroenterology* **145**, 954–965 (2013).
70. Pandolfino, J. E. *et al.* Achalasia: a new clinically relevant classification by high-resolution manometry. *Gastroenterology* **135**, 1526–1533 (2008).
71. Nicodeme, F. *et al.* Adding a radial dimension to the assessment of esophagogastric junction relaxation: validation studies of the 3D-eSleeve. *Am. J. Physiol. Gastrointest. Liver Physiol.* **303**, 275–280 (2012).
72. Bogte, A., Bredenoord, A. J., Oors, J., Siersema, P. D. & Smout, A. J. Relationship between esophageal contraction patterns and clearance of swallowed liquid and solid boluses in healthy controls and patients with dysphagia. *Neurogastroenterol. Motil.* **24**, 364–372 (2012).
73. Sweis, R., Anggiansah, A., Wong, T., Brady, G. & Fox, M. Assessment of esophageal dysfunction and symptoms during and after a standardized test meal: development and clinical validation of a new methodology utilizing high-resolution manometry. *Neurogastroenterol. Motil.* **26**, 215–228 (2014).
74. Nguyen, N. Q., Holloway, R. H., Smout, A. J. & Omari, T. I. Automated impedance-manometry analysis detects esophageal motor dysfunction in patients who have non-obstructive dysphagia with normal manometry. *Neurogastroenterol. Motil.* **25**, 238–245 (2013).
75. Rommel, N., Van Oudenhove, L., Tack, J. & Omari, T. I. Automated impedance manometry analysis as a method to assess esophageal function. *Neurogastroenterol. Motil.* **26**, 636–645 (2014).

Author contributions

Both authors contributed equally to all aspects of this manuscript.