Achalasia

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Abstract | Achalasia is a rare disorder of the oesophageal smooth muscle characterized by impaired relaxation of the lower oesophageal sphincter (LES) and absent or spastic contractions in the oesophageal body. The key pathophysiological mechanism is loss of inhibitory nerve function that probably results from an autoimmune attack targeting oesophageal myenteric nerves through cell-mediated and, possibly, antibody-mediated mechanisms. Achalasia incidence and prevalence increase with age, but the disorder can affect all ages and both sexes. Cardinal symptoms consist of dysphagia, regurgitation, chest pain and weight loss. Several years can pass between symptom onset and an achalasia diagnosis. Evaluation starts with endoscopy to rule out structural causes, followed by high-resolution manometry and/or barium radiography. Functional lumen imaging probe can provide complementary evidence. Achalasia subtypes have management and prognostic implications. Although symptom questionnaires are not useful for diagnosis, the Eckardt score is a simple symptom scoring scale that helps to quantify symptom response to therapy. Oral pharmacotherapy is not particularly effective. Botulinum toxin injection into the LES can temporize symptoms and function as a bridge to definitive therapy. Pneumatic dilation, per-oral endoscopic myotomy and laparoscopic Heller myotomy can provide durable symptom benefit. End-stage achalasia with a dilated, non-functioning oesophagus may require oesophagectomy or enteral feeding into the stomach. Long-term complications can, rarely, include oesophageal cancer, but surveillance recommendations have not been established.

The oesophagus is a hollow muscular tube that forms a conduit for the transmission of ingested food from the mouth to the stomach. A sphincter controls each end of the oesophagus: the upper oesophageal sphincter (UES) separates the oropharynx from the oesophagus, and the lower oesophageal sphincter (LES) forms a barrier between the intrathoracic and intra-abdominal compartments of the gut (FIG. 1). Volitional initiation of a swallow in the skeletal muscle oropharynx results in UES opening and transmission of the ingested bolus into the oesophagus. The bolus travels through the oesophagus primarily by gravity in the upright position, and an oesophageal stripping wave from circular muscle contraction forms a peristaltic sequence that clears any remnant content into the stomach. This peristaltic wave starts in the proximal skeletal muscle oesophagus and is transmitted into the distal smooth muscle oesophagus through the muscle fibres themselves, and through intermediary ganglia that control excitation and inhibition within the oesophageal smooth muscle. The LES relaxes concurrently with UES opening, and regains its closed resting tone when the peristaltic sequence arrives at the level of the lower sphincter.

Achalasia is defined as the presence of oesophageal outflow obstruction due to impaired relaxation of the LES with absent or spastic contractions in the oesophageal body in the absence of structural obstruction in the oesophageal body or oesophagogastric junction (EGJ)[1,2]. The clinical manifestations of achalasia are a consequence of obstruction in oesophageal transit owing to abnormal swallow-induced LES relaxation[3]. Incomplete LES relaxation and abnormal oesophageal body peristalsis can also be seen in pseudoachalasia, which needs to be distinguished from achalasia[4].

At its core, the pathophysiological abnormality in achalasia is loss of inhibitory nerve function in the smooth muscle oesophagus. The main hypothesis is that it results from an autoimmune reaction that targets oesophageal myenteric neurons through a cell-mediated and a, possibly antibody-mediated, attack against an antigen, which has not yet been fully identified, in genetically predisposed patients[5–8]. Infectious and degenerative hypotheses have also been postulated, but no definitive evidence has been reported[9–11]. Three subtypes of achalasia can be distinguished on the basis of manometric assessment of oesophageal motility patterns. Achalasia type 1 is characterized by 100% failed contractions and no oesophageal pressurization; type 2 is defined as pan-oesophageal pressurization occurring with at least 20% of swallows; and type 3 is defined as

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the presence of premature contraction for at least 20% of the swallows with premature contraction defined as distal latency <4.5 s. In terms of neuronal dysfunction, achalasia types 1 and 2 are both characterized by loss of ganglion cells (aganglionosis)[12], with a gradient of more severe loss in type 1 achalasia[13], whereas in type 3, inhibitory neuron function is impaired without clear neuronal loss, possibly mediated by cytokine-induced alterations in gene expression.

In this Primer, we discuss the epidemiology, pathophysiology, diagnosis and management of achalasia. We also summarize effects of this disorder on patient quality of life and research areas that are in need of further study.

Epidemiology

The annual incidence of achalasia is estimated at 1–5 cases per 100,000 individuals with a prevalence of 7–32 cases per 100,000 individuals[14–17]. Incidence rates are comparable across countries and regions using similar epidemiological methodology and do not differ by ethnicity[18–20]. A 2021 US study using commercial insurance and Medicare claims data suggested that incidence and prevalence could be higher than previously thought, with incidence of 10 and 26 per 100,000 individuals, and prevalence of 18 and 162 per 100,000 individuals in the two databases, respectively[20]. On the basis of these data, the economic burden of achalasia exceeded $408 million in 2018 in the USA.

Achalasia can occur at any age, but incidence and prevalence increase with age, and the mean age at diagnosis is >50 years[17,19,20]. Incidence (2.2 per 100,000 persons) and prevalence (15.3 per 100,000 persons) in men and women are similar[15]; however, in the US study, the incidence was higher (21.0 per 100,000 person) in women aged 45–64 years than in men of similar age, but no sex-specific difference was observed in younger patients[20].

The delay between onset of the first symptoms and a diagnosis of achalasia can be as long as several years, although use of high-resolution manometry (HRM) may facilitate an earlier diagnosis[21]. For example, the incidence of achalasia in the Chicago area was twofold to threefold higher in 2004–2014, after the introduction of HRM for achalasia diagnosis, compared with previous estimates when conventional manometry was used[18]. However, these epidemiological changes cannot be attributed solely to the adoption of HRM, as a true increase in disease incidence, an increased disease awareness related to the introduction of modern diagnostic tools and the availability of new therapeutic modalities could also have contributed[22].

Mechanisms/pathophysiology

In achalasia, the pharyngeal swallow effort and proximal oesophageal peristalsis are generally normal, as the disease primarily affects LES relaxation, with compromising consequences on coordination and strength of distal oesophageal circular muscle function and impaired contractility of longitudinal muscle layers. Thus, swallowed boluses traverse the pharynx and upper part of the oesophagus without difficulty, arriving in the non-functioning lower two-thirds of the oesophagus, which dilates and retains content because of insufficient contractile emptying force and an obstructing non-relaxing LES. In early achalasia, retained oesophageal muscle tone and hydrostatic forces generated by the ingested bolus can overcome the sphincteric resistance such that LES obstruction is incomplete and adequate nutrition is maintained; however, the oesophagus never completely empties. In later disease stages, emptying comprises only a small stream of fluid seeping through the obstructed, closed sphincter[23].

Abnormal neural control of motor function

Failing neural inhibition of oesophageal motility is the prime reason for abnormal peristalsis and incomplete LES relaxation in achalasia[24] (FIG. 2). An inverse relationship exists between the extent of neural inhibition and the propagation velocity of oesophageal peristalsis during swallowing: the lower the inhibition, the faster the propagation. In the extreme case of near absent or absent inhibition as in achalasia, non-peristaltic simultaneous oesophageal body contractions occur that eventually lead to aperistalsis[25].

Deglutitive inhibition can be evaluated using multiple rapid swallows (MRS), an adjunctive provocative manoeuvre routinely performed during oesophageal HRM. Under normal circumstances, repetitive swallowing during MRS inhibits oesophageal smooth muscle contractions and induces complete LES relaxation. The final swallow of the MRS series is followed by a powerful peristaltic sequence in the oesophageal body and re-establishment of LES tone[26] (FIG. 3). In patients with achalasia, during MRS, LES relaxation can be incomplete. Discoordinated or simultaneous oesophageal body contractions can occur in early-stage achalasia, and aperistalsis and oesophageal pressurization occurs in late stages of achalasia[27,28].

Both in vivo and in vitro experiments have evaluated the mechanisms that underlie abnormal neural control in achalasia. In vivo, intravenously administered recombinant haemoglobin, which inactivates nitric oxide, produces simultaneous oesophageal body contractions and failed LES relaxation similar to that seen in achalasia[29], establishing a role for nitric oxide in inhibitory neural transmission. In vitro, in LES specimens from patients

with achalasia, inhibitory neurons containing vasoactive intestinal peptide (VIP) and nitric oxide synthase were found to be reduced or absent[30,31]. Circular LES muscles strips showed an abnormal contractile response to electrical field stimulation owing to lack of activation of nitric-oxide-containing inhibitory neurons[32]. Furthermore, cholecystokinin, which normally relaxes the LES through activation of inhibitory nerves, provokes paradoxical LES contraction in achalasia[33]. By contrast, excitatory cholinergic nerves were found to be partially preserved in achalasia[34].

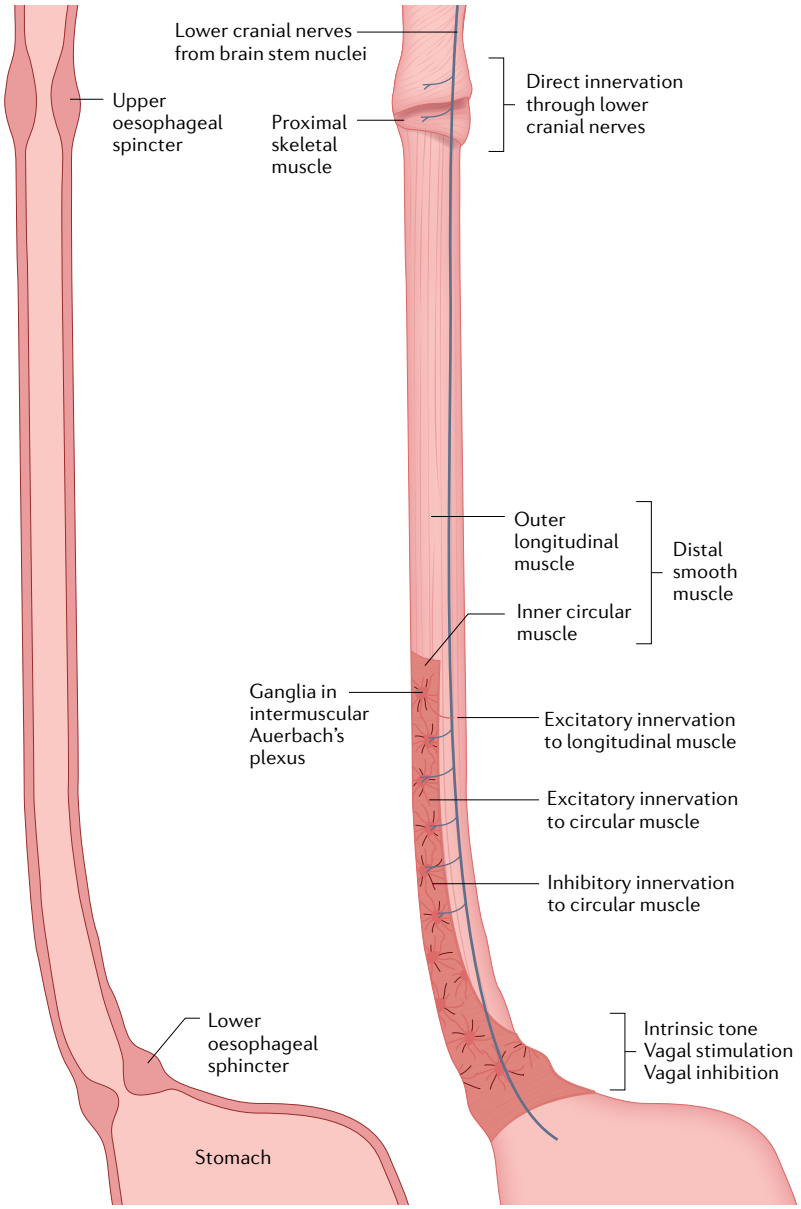

Fig. 1 | **Normal oesophageal physiology and innervation.** The upper oesophageal sphincter and the proximal third of the oesophagus consist of skeletal muscle under volitional control through direct cranial nerve innervation. The remainder of the tubular oesophagus consists of smooth muscle, with an outer longitudinal layer and an inner circular layer. A nerve plexus (Auerbach's plexus) between the two muscle layers has cranial input, and both excitatory and inhibitory post-ganglionic neurons innervate the circular muscle, but only excitatory neurons innervate longitudinal muscle. Excitation induces contraction via cholinergic neurotransmitters, and inhibition via nitric oxide as the predominant neurotransmitter is crucial for the timing of peristalsis as well as relaxation of the lower oesophageal sphincter (LES). The LES has resting pressure that keeps the lumen closed at rest, determined by a combination of intrinsic tone and vagal stimulation.

Aetiopathogenesis

Achalasia is an autoimmune disease that affects oesophageal myenteric neurons with confirmed cell-mediated and possible antibody-mediated mechanisms. Autoimmune disorders, including Sjögren syndrome, type 1 diabetes mellitus and hypothyroidism, are frequently encountered in patients with achalasia, supporting autoimmune mechanisms in achalasia pathophysiology[35–38]. In a large European cohort of patients with idiopathic achalasia, comorbid allergic and autoimmune disorders, as well as viral infections (in particular with varicella zoster virus) before symptom onset, were observed[39]. Genetic predisposition also has a role, as an eight-amino-acid insertion in the cytoplasmic tail of HLA-DQβ1 is a risk factor for achalasia[40,41]. This is more prevalent in type 1 achalasia than other subtypes and less common in northern European patients (around 6–7%) than in southern Europeans (~16%)[42]. Thus, loss of myenteric plexus neurons involves autoimmunity, viral infection and genetic predisposition (FIG. 4).

Cell-mediated autoimmunity. Oesophageal biopsy samples in achalasia demonstrate myenteric plexus neurons surrounded by inflammatory cells, predominantly T cells, eosinophils, plasma cells, B cells, mast cells and macrophages[6,43,44]. Immunohistochemical staining indicates that the T cells are $CD3^+$, cytotoxic $CD8^+$ and tumour necrosis factor (TNF)-positive (TNF is a cytokine able to promote the killing of various intracellular infectious viruses, bacteria and parasites) rather than a regulatory phenotype[45]. Inflammation is seen in all regions of the oesophagus and in all three achalasia subtypes. Other immune cells, including eosinophils and mast cells, also contribute to the inflammatory response[46]. Eosinophils infiltrate both the muscularis externa and the muscularis propria[47], and degranulating eosinophils release toxic proteins capable of destroying myenteric neurons, leading to impaired oesophageal motility as hypothesized in patients with eosinophilic oesophagitis, who showed an increase in achalasia diagnoses[48]. Infiltration of mast cells, both at the LES muscle and in the myenteric plexus[49], leads to a decrease in interstitial cells of Cajal, neuronal nitric oxide synthase-positive cells and S-100-positive cells of neural crest origin[50]. The observation of these specific cells involved in extracellular matrix turnover, apoptosis and fibrosis, as well as the systemic inflammatory autoimmune component (increased numbers of circulating T helper 22 (T_H22), T_H17, T_H2 and T_H1 cells), associated with the presence of specific anti-myenteric autoantibodies and herpes simplex virus 1 (HSV-1) infection, all support the concept of autoimmune mechanisms that target the oesophageal myenteric plexus in achalasia[5].

Antibody-mediated autoimmunity and serum cytokines. The immune attack on the myenteric plexus is associated with the production of antineuronal antibodies by plasma cells and B cells[51–53]. Antibodies to myenteric

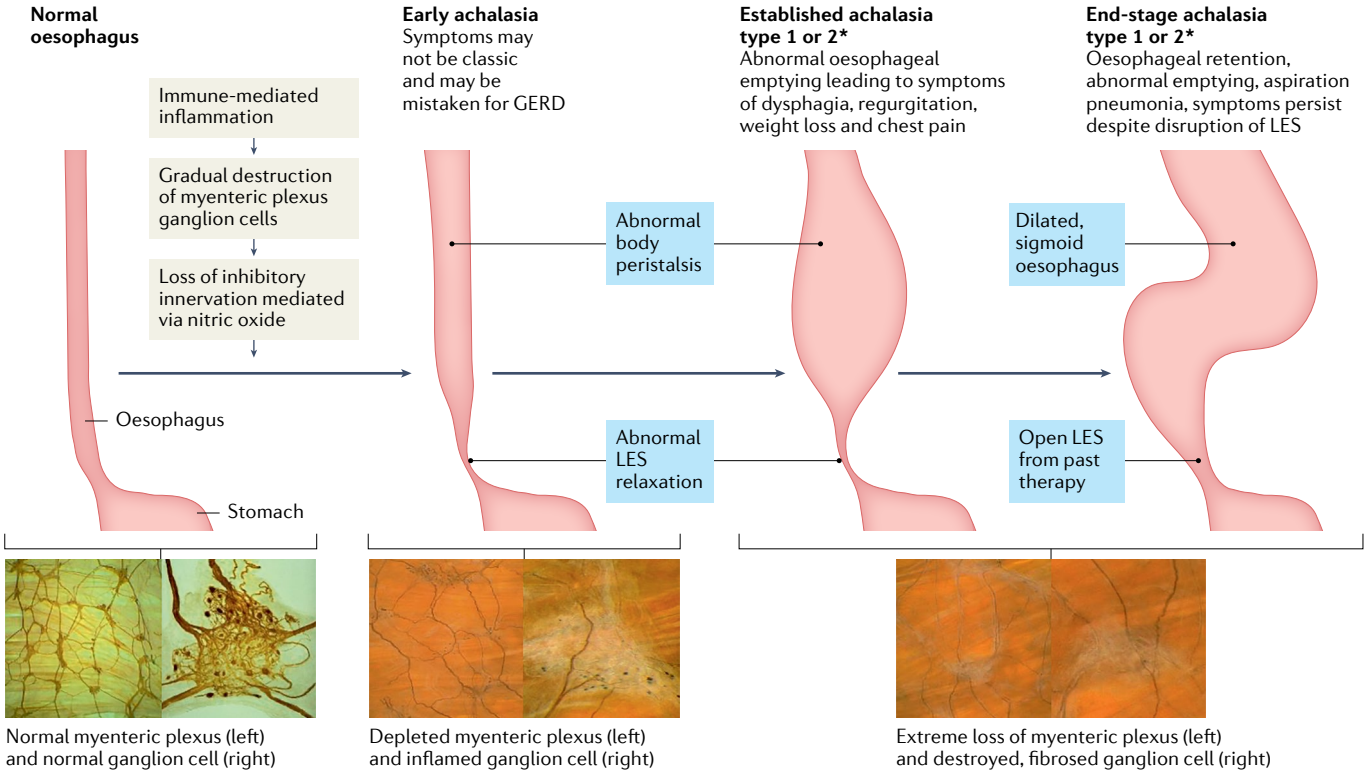

Fig. 2 | **Oesophageal manifestations and natural history of achalasia.** The core pathophysiological abnormality in achalasia is loss of predominantly inhibitory nerve control of the oesophagus, leading to oesophageal outflow obstruction from loss of swallow-induced relaxation of the lower oesophageal sphincter (LES), and loss of or abnormal oesophageal body peristalsis. Symptoms are a consequence of this obstructive effect, which leads to progressive dilation of the oesophageal lumen over time. Histopathological analysis shows inflammation and depletion of oesophageal ganglia and neurons in early achalasia and replacement with fibrosis in later stages of achalasia. End-stage achalasia results in a dilated, sigmoid-shaped oesophagus that may not empty even if the LES is open from adequate therapeutic disruption. GERD, gastro-oesophageal reflux disease. *Achalasia type 3 may not manifest oesophageal dilation, and its natural history is largely unknown.

neurons can be found in patients with achalasia with *HLA-DQA1*0103* and *HLA-DQB1*0603* alleles[51]. However, the specificity of antineuronal antibodies for achalasia has been questioned, as these antibodies do not selectively target oesophageal myenteric neurons and have also been detected in patients with gastro-oesophageal reflux disease (GERD)[8]. Thus, these antibodies may be a consequence of the inflammatory process and nonspecific rather than a causative factor in achalasia pathogenesis.

Viral infection. Viral DNA and virus-targeted antibodies have been found in oesophageal tissue and in the serum, respectively, of patients with achalasia[54,55], involving HSV-1, measles virus and human papillomavirus[11,54].

HSV-1 is a neurotropic virus with a predilection for squamous epithelium. Viral DNA from HSV-1 was demonstrated in oesophageal tissue from patients with achalasia, and T cells from that tissue proliferated and released cytokines following exposure to HSV-1 antigens[11,55]. However, other investigators did not find HSV-1 or other viruses in achalasia oesophageal specimens[56]. HSV-1 DNA has also been found in oesophageal tissue from individuals without achalasia. These findings have led to the hypothesis that HSV-1 can cause a persistent immune activation that damages oesophageal enteric neurons only when triggered by a yet unknown factor and only in genetically susceptible individuals[57]. Thus, not all patients infected with predisposing viruses develop achalasia, indicating the potential role of genetic factors to make some individuals more susceptible to achalasia than others[58].

Genetics. Immunogenetic studies report an association between *HLA-DQw1*, *HLA-DQA1* and *HLA-DQB1*, and achalasia, with *HLA-DQB1* being the most commonly reported[53,59]. Antibodies to myenteric neurons have been found in serum samples from patients with achalasia, particularly those with *HLA-DQA1*0103* and *HLA-DQB1*0603* alleles[51]. As achalasia has associations with HLA genes, affected siblings and parents are occasionally encountered[60], although familial achalasia is uncommon[61]. Achalasia can be part of a genetic syndrome, such as the Algrove syndrome (also termed AAA syndrome, which involves achalasia, alacrimia and adrenal insufficiency) from missense or truncation mutation on chromosome 12 (REF.[62]). Achalasia can occur in individuals with intellectual disability owing to chromosome 2 mutations and in those with Down syndrome[63]. Genetic syndromes may be identified more often in children with achalasia.

Furthermore, in some studies, signalling pathway abnormalities have been reported in idiopathic achalasia, which might be related to the underlying pathological neuronal mechanism and reduced activity of interstitial cells of Cajal[64,65]. Transcriptomic analysis of achalasia tissues identified dysregulated expression of specific genes, such as downregulated expression of *KIT* and upregulated expression of *INPP4B*, the latter being linked to AKT pathway regulation[66].

Achalasia subtypes

Pathophysiology. Achalasia is a heterogeneous disorder and the aetiopathogenesis, pathophysiology and symptomatic profiles of achalasia subtypes vary[67].

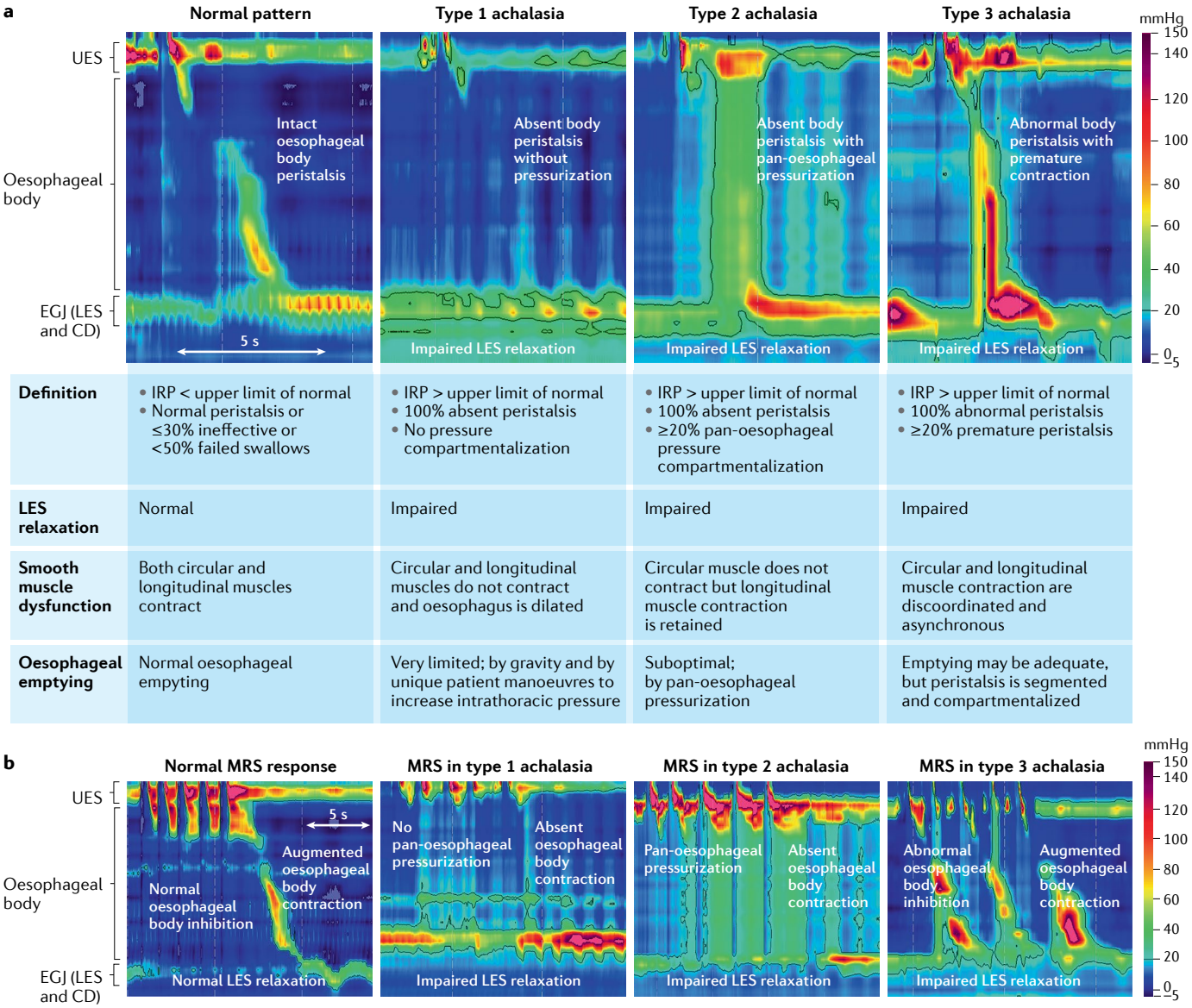

Fig. 3 | **Achalasia subtypes based on high-resolution manometry.** **a** | High-resolution manometry (HRM) patterns identifying oesophageal achalasia during liquid swallows and according to Chicago classification v4.0 (REF.[3]). The common manometric abnormality on HRM is an abnormal integrated relaxation pressure (IRP) above the upper limit of normal for the HRM system used. However, IRP may be within normal limits in type 1 achalasia. The oesophageal body motor pattern determines the three subtypes. In type 1 achalasia, peristalsis and pressurization are absent. In type 2 achalasia, pan-oesophageal pressurization occurs in at least 20% of swallows. In type 3 achalasia, non-peristaltic oesophageal body contractions are observed with ≥20% premature contractions (with distal latency <4.5 s). The patterns of smooth muscle contractility and mechanisms of oesophageal emptying also differ between the three subtypes. **b** | Multiple rapid swallows (MRS) for assessment of deglutitive relaxation in achalasia[26–28]. During repetitive swallowing in the healthy oesophagus, there is profound inhibition of oesophageal body contraction and relaxation of the lower oesophageal sphincter (LES). After the last swallow of the sequence, there is an augmented contraction sequence and re-establishment of LES tone. Inhibitory dysfunction manifests as varying degrees of incomplete LES relaxation during MRS in the achalasia subtypes. In type 3 achalasia, LES relaxation is intermittent. Oesophageal body contraction is absent in type 1 and type 2 achalasia, but with pan-oesophageal pressurization in type 2 achalasia. In type 3 achalasia, incomplete inhibition may manifest as a breakthrough contraction during repetitive swallowing. CD, crural diaphragm; EGJ, oesophagogastric junction; UES, upper oesophageal sphincter.

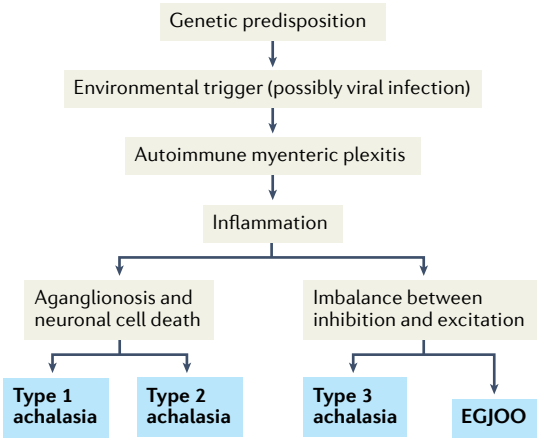

Fig. 4 | **Two possible pathways of pathogenesis differentiate achalasia subtypes.** In genetically predisposed individuals, an environmental trigger, perhaps a viral infection, is thought to initiate a cell-mediated immune response as well as an antibody-mediated response that preferentially attacks inhibitory ganglia and neurons in the oesophageal neural plexi. If complete loss of ganglia and neurons results, abnormal lower oesophageal sphincter (LES) relaxation coexists with absent contraction in the oesophageal body, characterizing potentially type 2 achalasia in early stages, and type 1 achalasia as the disease progresses. If inflammation ensues without complete loss of inhibitory control, imbalance between inhibition and excitation results in premature or spastic oesophageal body contractions characterizing type 3 achalasia or even intact oesophageal body contractions in conjunction with abnormal LES relaxation characterizing oesophagogastric junction outflow obstruction (EGJOO).

Abnormal LES relaxation is a prerequisite finding, but oesophageal body motility patterns differ between the three achalasia subtypes defined with HRM[3]. Impairment of LES relaxation occurs in association with absent peristalsis (type 1 achalasia), pan-oesophageal pressurization (type 2), premature (spastic) distal oesophageal contractions (type 3) (FIG. 3), or even preserved peristalsis, all of which are compatible with achalasia[68].

During normal peristalsis, circular and longitudinal smooth muscle in the oesophageal body contracts synchronously. Both circular and longitudinal muscle contraction are substantially compromised in type 1 achalasia, with minimal to no longitudinal muscle contraction. By contrast, in type 2 achalasia, strong longitudinal muscle contraction, part of the basis for pan-oesophageal pressurization, is preserved. Considerable discoordination between contracting circular and longitudinal muscles characterizes type 3 achalasia[69]. Thus, smooth muscle contraction, particularly longitudinal muscle contraction patterns, differ between the three achalasia subtypes.

Mechanisms of oesophageal emptying are also distinct. In type 1 achalasia, oesophageal emptying occurs with gravity and from unique measures that the patient develops to increase intrathoracic pressure above the LES closing pressure. By contrast, in type 2 achalasia, pan-oesophageal pressurization against a closed LES is the main mechanism of intermittent oesophageal emptying, generated by a combination of preserved proximal striated muscle contraction, longitudinal muscle contraction and non-occlusive distal circular muscle contraction against augmented EGJ outflow obstruction (EGJOO)[69]. Interestingly, impedance recordings suggest that oesophageal transit can be adequate but segmented and discoordinated in type 3 achalasia[69,70]. When challenged with MRS, type 1 achalasia exhibits no LES relaxation, type 2 may augment LES pressure and type 3 may manifest LES relaxation to a near normal extent[27,28].

Aetiopathogenesis. The prevailing hypothesis is that both type 1 and type 2 achalasia are the consequence of a cytotoxic immune attack leading to progressive myenteric plexus neuronal death without selectivity among subsets of myenteric plexus neurons[5–11] (FIG. 2). By contrast, patients with type 3 achalasia have an immune response that affects neuronal function but without causing neuronal death[12,13]. Serum from patients with type 3 achalasia can induce downregulation of nitric oxide synthase expression and increased cholinergic sensitivity without affecting the number of neurons[71]. Circulating IL-8 can mediate this response, suggesting that local cytokine release could induce an imbalance between inhibitory and excitatory post-ganglionic neuronal function in type 3 achalasia. Finally, a progressive plexopathy is also recognized, evolving from achalasia with preserved peristalsis, to type 2 achalasia and, subsequently, to type 1 achalasia[68].

Diagnosis, screening and prevention

Clinical presentation

The most common symptoms reported by patients with achalasia consist of dysphagia for both solids and liquids, and regurgitation of undigested food and saliva, especially while lying flat at night, which can result in weight loss and, less frequently, bronchitis or relapsing pneumonias[72]. Although counterintuitive, achalasia can also exist in individuals with morbid obesity, likely due to associated oesophageal hyposensitivity, which may limit the sensation of dysphagia[73]. Regurgitation of undigested food can be misidentified as vomiting, leading to suspicion of a gastric disorder rather than an oesophageal process. Chest pain may also be reported in all subtypes of achalasia, but particularly type 3 achalasia[23,68]. The exact mechanism underlying chest pain remains unclear but could include fermentation of food retained in the oesophagus to acidic by-products that stimulate chemoreceptors, stasis-related oesophageal inflammation, spastic and discoordinated smooth muscle contraction and/or oesophageal hypersensitivity[1,2,68]. Presenting symptoms in children are similar to those in adults with achalasia. Additionally, coughing and/or choking during eating, recurrent aspiration pneumonias, feeding difficulties, food refusal and failure to thrive may be present[74,75]. The Eckardt score quantifies the four cardinal achalasia symptoms (dysphagia, regurgitation, chest pain and weight loss) using a 4-point grading system[76] (TABLE 1), in which a score of ≤3 quantifies adequate treatment outcome. Despite lack of validation as a patient-reported outcome (PRO) measure, it is useful to record the Eckardt score at initial achalasia diagnosis as

a measure of symptom severity[77,78]. Of note, patients can rarely present with symptoms that mimic GERD, such as heartburn, chest pain and regurgitation, and may even be referred for anti-reflux surgery[79,80]. This may lead to disease progression and a more severe impairment of oesophageal anatomy and peristalsis from misdiagnosis and mismanagement as GERD[79].

Other benign disorders, including GERD, benign oesophageal strictures, eosinophilic oesophagitis, diffuse oesophageal spasm, hypercontractile oesophagus and neoplastic oesophageal diseases are more common causes of dysphagia and regurgitation than of true achalasia. Thus, oesophageal evaluation for achalasia is usually undertaken after upper endoscopy and/or barium radiography have ruled out alternative structural or mucosal mechanisms for symptoms. Presentation with chest pain or heartburn in combination with regurgitation may prompt a diagnosis of GERD, and trials of anti-reflux medications are common. In fact, achalasia is diagnosed in up to 2.5% of patients undergoing manometry before anti-reflux surgery[80], indicating that testing for achalasia needs to be performed when reflux-like symptoms do not improve despite anti-reflux medications.

Diagnostic modalities

Diagnosis of achalasia requires recognition of presenting symptoms as well as appropriate use and interpretation of diagnostic testing (FIG. 5). The tests commonly used for reaching a correct diagnosis include upper endoscopy, manometry and oesophagography.

Upper endoscopy. Endoscopy has a low diagnostic yield in the identification of achalasia and its primary role is in ruling out alternative mechanisms for oesophageal obstruction[2]. However, the procedure might provide clues to the presence of achalasia, including the presence of fluid or food residue within a dilated oesophagus, and a puckered, tight EGJ that resists but does not obstruct the passage of the endoscope (FIG. 6). Other endoscopic signs include the oesophageal rosette sign and the champagne glass sign[81,82]. Frothy saliva and candidiasis within a non-dilated oesophagus may raise suspicion for achalasia[83].

Manometry. Achalasia is diagnosed on the basis of manometric demonstration of abnormal LES relaxation and aperistalsis (FIG. 5). HRM is the modern standard for this assessment and is easier to perform than conventional manometry, with good to excellent inter-rater and intra-rater agreement for achalasia subtypes, and it is preferred by learners as well as experts[84,85]. HRM uses a classification scheme termed the Chicago classification to define disorders of EGJ function and oesophageal peristalsis, which was revised and updated in 2021 (REF.[3]). This classification is based on the hierarchical assessment of adequacy of LES–EGJ relaxation followed by evaluation of oesophageal body peristalsis. By using specific HRM metrics, clinically relevant motor patterns can be reliably identified, including achalasia, EGJOO, distal oesophageal spasm, hypercontractile oesophagus, ineffective oesophageal motility and absent contractility[3]. Thus, the application of HRM using the Chicago classification in clinical practice increases the diagnostic yield and emphasizes the role of HRM in selecting the optimal therapeutic approach in achalasia, with the ultimate goal of improving patient outcome[86,87]. Whenever possible, HRM should be performed in the absence of opioid or other medications that may alter oesophageal motility. The key metric for adequacy of LES relaxation is the integrated relaxation pressure (IRP), which describes nadir LES pressures over 4 s during a 10 s window that includes swallow-induced LES relaxation. The sensitivity of the IRP over the upper limit of normal was 98% for a diagnosis of abnormal LES relaxation, with a specificity of 96%[88]. Compared with conventional manometry, use of the IRP from HRM increased the diagnostic yield from 12% to 26% in patients with dysphagia in a randomized multicentre study[21]. The median IRP from 10 swallows of 5 ml of water in the supine position during HRM is the current standard, and the upper limit of normal differs depending on the HRM system used[3,89].

In addition to abnormal LES relaxation, oesophageal smooth muscle contraction is considerably altered in achalasia, including absence of peristaltic contractions, although premature or spastic contractions can also occur. The pattern of pressurization or contraction within the smooth muscle oesophageal body determines achalasia subtypes (FIG. 3), which has implications for disease management[87]. Absence of peristalsis without pressurization is seen in type 1 achalasia, in which the IRP may be manometrically normal in some instances, and alternative tests are needed to confirm achalasia in the presence of compatible symptoms[90] (FIG. 5). Pan-oesophageal pressurization in ≥20% of supine water swallows defines type 2 achalasia, which has the best management outcomes among all achalasia subtypes[86,87]. Contractility is retained in type 3 achalasia, but peristalsis is not normal; premature and/or spastic contractions are seen in ≥20% of the swallows[3]. Response to standard therapy can be substandard in type 3 achalasia[86], although tailored extended per-oral endoscopic myotomy (POEM) may provide improved symptom relief[91].

Some patients can present with achalasia-like symptoms that respond to achalasia treatment, but with intact oesophageal body peristalsis and evidence of oesophageal outflow obstruction in the form of an abnormal IRP (termed EGJOO)[92]. Conceptually, EGJOO could be related to compromised deglutitive EGJ relaxation (motor EGJOO) or to structural EGJ abnormalities

Table 1 | **Eckardt score**

Symptom	Score			
	0	1	2	3
Dysphagia	None	Occasional	Daily	Every meal
Regurgitation	None	Occasional	Daily	Every meal
Chest pain	None	Occasional	Daily	Every meal
Weight loss (kg)	None	<5	5–10	>10

Scores are added up to generate a total score between 1 and 12. Adapted with permission from REF.[76], Elsevier.

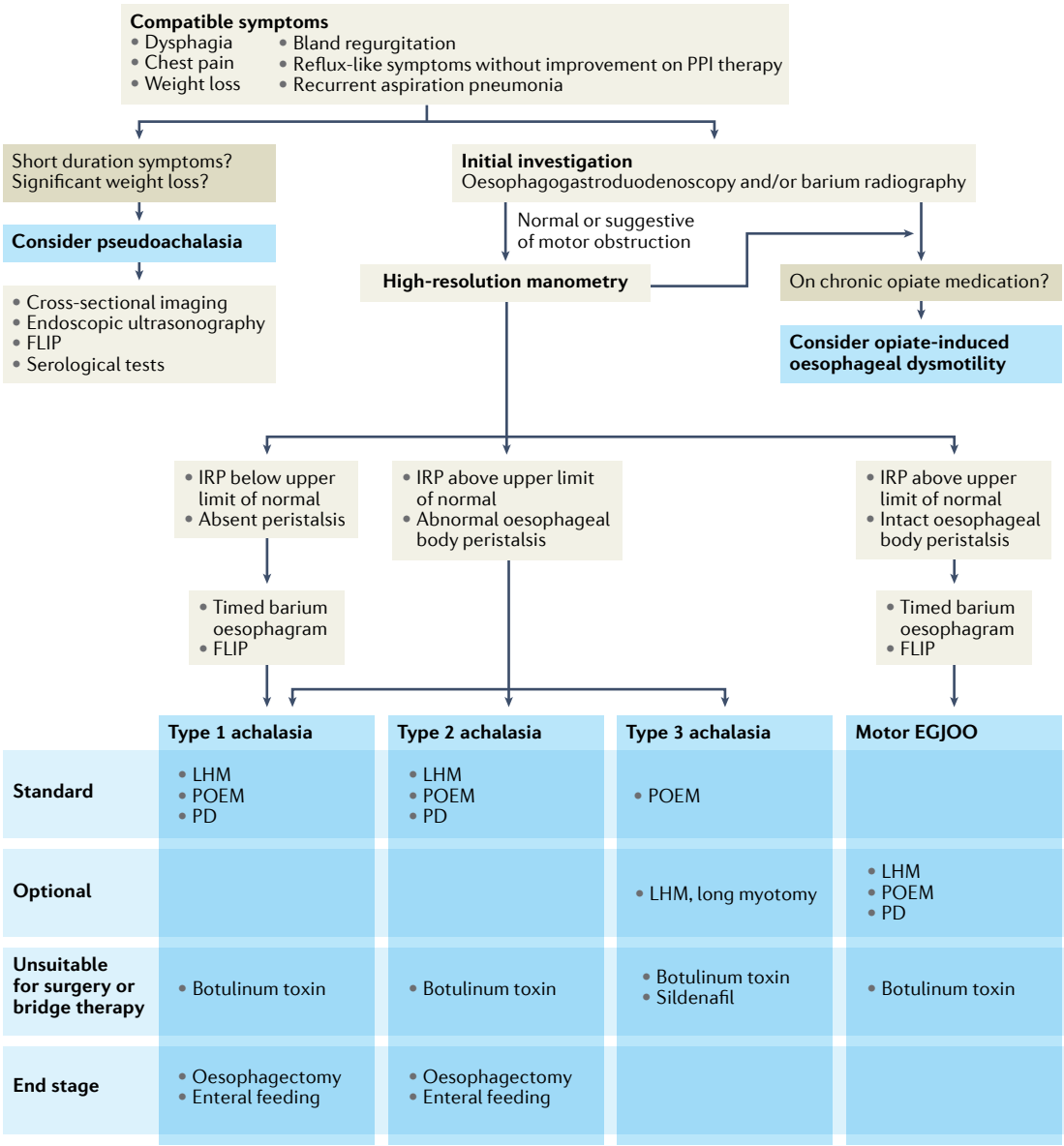

Fig. 5 | **Diagnostic and management algorithm for achalasia.** In the presence of compatible symptoms (particularly dysphagia, regurgitation, chest pain and weight loss), upper endoscopy serves to exclude structural aetiologies, as well as pseudoachalasia from distal oesophageal or proximal gastric neoplastic processes. Opioid use can mimic achalasia, particularly type 3 achalasia and oesophagogastric junction outflow obstruction (EGJOO). The gold standard for diagnosis of achalasia is high-resolution manometry (HRM). HRM findings can also subtype achalasia, with management implications. Type 1 achalasia needs to be suspected even when the integrated relaxation pressure (IRP) is within normal limits on HRM, and adjunctive tests (timed barium oesophagram, functional lumen imaging probe (FLIP)) can be valuable in this regard. These adjunctive tests can also help to differentiate motor EGJOO, which can respond to achalasia treatments, from structural EGJOO or artefact. Definitive achalasia management requires disruption of the lower oesophageal sphincter (LES), using forceful dilation (pneumatic dilation (PD)) or myotomy (laparoscopic Heller myotomy (LHM) or per-oral endoscopic myotomy (POEM)). Botulinum toxin injection is an option for patients who are unsuitable for surgical intervention, and as a bridge to definitive therapy. Oesophagectomy or enteral feeding through a gastrostomy tube may be needed in end-stage achalasia with a dilated, non-functioning oesophagus that may not empty despite an open LES. PPI, proton pump inhibitor.

associated with mechanical obstruction (that is, fundoplication or bariatric surgery, cancer or other infiltrative processes, luminal stricture or extraluminal compression due to para-oesophageal hernia). Whether confirmed motor EGJOO without mechanical obstruction represents early achalasia in which oesophageal body features have not yet developed or whether it is a different entity remains under debate[92,93]. Clinically, it is imperative that structural mechanisms and artefactual IRP elevations are ruled out before considering achalasia-like management for EGJOO. Persistence of IRP elevation on upright swallows, compartmentalization of intrabolus pressure in the distal oesophagus and obstructive features on provocative tests during HRM support a diagnosis of

EGJOO. When available, amyl nitrite inhalation during HRM can demonstrate LES relaxation in achalasia or motor EGJOO, which can help distinguish achalasia from opioid-induced EGJOO or IRP elevation due to non-achalasia mechanisms[94,95]. However, supporting evidence from barium radiography or functional lumen imaging probe (FLIP) is essential for a conclusive diagnosis of EGJOO[3]. When the diagnosis is inconclusive, a therapeutic trial of botulinum toxin injection into the LES during endoscopy can be useful[96], as a symptom response might indicate motor obstruction that could respond to achalasia treatment for durable symptom relief (FIG. 5).

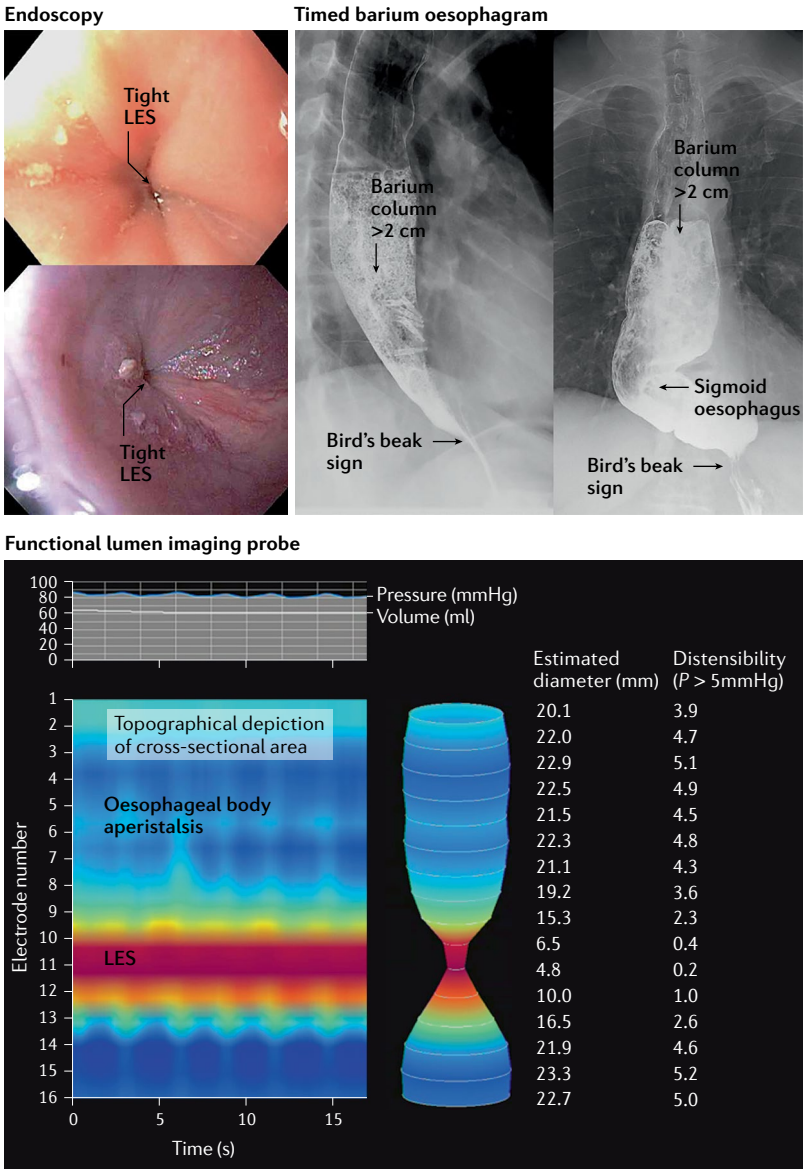

Fig. 6 | **Adjunctive tests in the diagnosis of achalasia.** Endoscopy may demonstrate a dilated oesophagus with food or frothy saliva residue and a tight and puckered lower oesophageal sphincter (LES) that offers modest resistance to endoscope passage[2]. A timed barium oesophagram (TBE) reveals abnormal oesophageal emptying, typically measured as a barium column >2 cm in the upright position 5 min after administration of 200 ml of low-density barium sulfate[98–100]. The bird's beak sign of the oesophagus is used to refer to the tapering of the inferior oesophagus in achalasia. In the advanced stage of achalasia, a TBE may show a sigmoid-shaped oesophagus, in which the oesophageal lumen is substantially dilated, swerved and rotated. Functional lumen imaging probe (FLIP) uses impedance planimetry to measure cross-sectional areas within the oesophageal lumen[101]. The ratio between cross-sectional area and distending pressure at the level of the LES determines the distensibility index, which is typically <2 mm^2/mmHg in obstructive processes. Topographical depiction of cross-sectional area in the oesophageal body can be used to demonstrate secondary peristalsis, termed FLIP panometry. The oesophageal body demonstrates no contraction (aperistalsis) in achalasia type 1 and type 2 (as shown here). By contrast, spastic contractions and retrograde contractions may be seen in type 3 achalasia. A normal contraction pattern consists of anterograde contractions occurring at the rate of six contractions per minute.

Barium radiography. Barium radiography, particularly the timed barium oesophagram (TBE), has diagnostic and prognostic value in achalasia. A standard barium swallow may demonstrate a dilated oesophagus with a tapered 'bird's beak' EGJ, but has suboptimal performance characteristics for diagnosis of oesophageal motility disorders[97]. In patients with achalasia, a 13 mm diameter barium pill may become trapped and obstruct the EGJ. In a study comparing swallows of liquid barium alone with swallows of a combination of liquid barium plus a 13 mm barium pill, combined liquid barium and tablet increased diagnostic yield from 79.5% to 100% in patients with untreated achalasia and from 48.9% to 60% in patients with EGJOO, highlighting the complementary role of the barium pill in identifying achalasia as well as mechanical obstruction at the EGJ[98]. For TBE, the patient rapidly drinks 200 ml of low-density barium sulfate while upright, and X-ray films are obtained 1, 2 and 5 min thereafter[98,99] (FIG. 6). In an analysis of TBE data from a large cohort of patients with confirmed achalasia and individuals without achalasia but dysphagia presentations, a barium column height of 5 cm at 1 min showed the highest sensitivity of 86% and specificity of 71% in differentiating achalasia from non-achalasia oesophageal disorders, whereas a height of 2 cm at 5 min had a sensitivity of 80% and specificity of 86%[98]. TBE findings are reproducible with excellent inter-observer agreement, and can predict the likelihood of future symptom recurrence after achalasia therapy[99,100]. Thus, TBE can be used to adjudicate inconclusive HRM findings, especially in the context of EGJOO, and to assess adequacy of achalasia management (FIG. 5).

Functional lumen imaging probe. In the past 5 years, the FLIP, an endoscopic device consisting of a distensible balloon containing a catheter with several pairs of electrodes and a pressure sensor that simultaneously measures the cross-sectional area and pressure within a hollow viscus, has become a valuable complementary tool in the diagnosis of EGJ obstruction[101]. This advanced imaging system is able to study the biomechanical properties of luminal organs, in particular, the oesophagus and the EGJ. EGJ distensibility measured using FLIP can reliably diagnose achalasia even when EGJ relaxation is manometrically normal[90,102]. FLIP may detect an abnormal response to oesophageal distension in 50% of patients diagnosed with ineffective oesophageal motility (IEM) or normal HRM findings[103]. EGJ metrics (distensibility index and diameter) from FLIP studies outperform both supine and upright IRP measurements when compared with barium retention on TBE in detecting obstruction[104] (FIG. 6). Furthermore, FLIP can characterize achalasia subtypes

Box 1 | **Features of pseudoachalasia**

The term pseudoachalasia has traditionally been applied to neoplasia-induced achalasia-like manifestations. However, structural changes and processes at the oesophagogastric junction (EGJ), such as tight fundoplication or hiatus hernia repair, laparoscopic gastric band or bariatric surgical procedures, can also result in similar achalasia-like manifestations.

Characteristics that can be associated with pseudoachalasia

- Manometric pattern can mimic type 1, type 2 or type 3 achalasia, or EGJ outflow obstruction
- Incomplete patterns are common
- Occurrence at >55 years of age
- Short duration of symptoms (<1 year)
- Substantial weight loss (>10 kg),
- Difficulty in negotiating endoscope through EGJ
- Evidence of neoplasia on biopsy from EGJ or gastric cardia
- Abnormal, irregular wall thickening on endoscopic ultrasonography or CT
- Positive serological tests (antineuronal nuclear antibodies (ANNAs; also known as anti-Hu antibodies))
- Detection of distant cancers (such as lung, kidney or pancreatic cancer) on CT
- History of previous surgery at hiatus (for example, laparoscopic fundoplication or laparoscopic gastric band)

by detecting non-occlusive oesophageal contractions that are not observed with HRM to varying degrees in achalasia subtypes, enabling additional subclassification of patients with oesophageal obstruction[105,106]. Thus, FLIP has value as a complementary test for diagnosis of achalasia and EGJ obstruction, especially when HRM is inconclusive[97] (FIG. 5).

Exclusion of pseudoachalasia

Local distal oesophageal cancer and proximal gastric cancer, as well as distant cancer (for example, small cell lung cancer) can cause oesophageal symptoms and motor findings similar to achalasia, prompting use of the term pseudoachalasia to describe these oesophageal manifestations. Short duration of dysphagia (typically <1 year), substantial weight loss and old age are suggestive of pseudoachalasia[4,107], and warrant cross-sectional imaging (for example, CT and/or MRI), or endoscopic ultrasonography as part of the evaluation[107,108] (BOX 1). Serological tests, such as antineuronal nuclear antibodies (anti-ANNA 1 and 2 antibodies, also termed anti-Hu antibodies) have high sero-positivity rates in patients with small cell lung cancer and are sometimes performed when pseudoachalasia is suspected[109]. Compared with achalasia, HRM findings in pseudoachalasia can be atypical or incomplete and may not fit achalasia subtypes[4]. The term pseudoachalasia was initially applied only to neoplasia mimicking achalasia, but it is now recognized that structural EGJ processes can also result in HRM patterns identical to those of achalasia[4,107]. Endoscopy may reveal mucosal obstructive lesions, reduced EGJ compliance or stricture when local cancer is the mechanism for pseudoachalasia, and endoscopic biopsy can confirm the diagnosis. Structural obstruction from a tight fundoplication/hiatus hernia repair, gastric band placed for weight loss, extrinsic compression or para-oesophageal hernia can also result in manometric findings similar to those of achalasia[110]. Chagas disease, an infection of the protozoan parasite *Trypanosoma cruzi*, which causes damage to the oesophageal myenteric plexus that results in partial or absent LES relaxation and mega-oesophagus, can mimic achalasia[111,112]. Opioid use can result in manometric patterns with obstruction, including EGJOO and type 3 achalasia, and amyl nitrite inhalation during HRM can be used to differentiate opioid-related syndromes from true achalasia[94]. Eosinophilic oesophagitis can overlap with achalasia in rare instances, and achalasia management may be needed to complement traditional eosinophilic oesophagitis treatments[113,114]. Congenital oesophageal stenosis in adults is an extremely rare disorder that can present as achalasia[115]. Finally, some patients with spastic oesophageal body motility (hypercontractile oesophagus and distal oesophageal spasm) may have an obstructive component similar to achalasia, and case reports exist of these spastic disorders transitioning to achalasia over time[116].

Screening and prevention

As achalasia is extremely rare, population-based screening is not feasible. Early diagnosis can be facilitated by maintaining a high index of suspicion, particularly by performing HRM, TBE or FLIP when oesophageal symptoms do not improve with symptomatic management, or when persisting symptoms do not have a clear explanation. However, there is an inherent delay in diagnosis, as clinical manifestations take time to develop to the degree that prompts patients to present for medical evaluation. No preventive measures for achalasia are known.

Management

The oesophageal motor dysfunction in achalasia is irreversible. Thus, repair of the defective oesophageal body contractility is unrealistic, and therapeutic efforts are focused on relief of EGJ obstruction to restore oesophageal emptying, relieve oesophageal symptoms, improve quality of life and reduce the risk of end-stage achalasia. Several options are available, from pharmacological approaches to endoscopic or surgical myotomy, which have varying levels of symptom benefit and adverse effects. In late stages of achalasia, a dilated and sigmoid oesophagus may not be salvageable, and oesophagectomy and/or enteral feeding are sometimes necessary.

Medical therapy

Oral pharmacological therapy. Calcium channel blockers, nitrates, anticholinergics and phosphodiesterase inhibitors have been used for treating achalasia in small and often uncontrolled studies[117–120]. Although these agents can reduce LES pressure and temporarily relieve dysphagia, they do not improve oesophageal peristalsis or enhance LES relaxation[121]. Furthermore, prominent adverse events, such as headache, hypotension and peripheral oedema, can occur, limiting continued use and resulting in poor compliance of agents such as calcium channel blockers[122]. As the clinical response to oral pharmacological agents is inconsistent, incomplete and short-lived, their use should be reserved for patients who are not candidates for invasive endoscopic or surgical therapy, or those who decline invasive therapy.

Botulinum toxin injection. Injection of botulinum toxin into the LES is a short-term option for symptom relief or until more-durable therapies can be administered[123,124]. Botulinum toxin impairs acetylcholine release, leading to inhibition of contraction of LES smooth muscle fibres, thereby lowering LES tone. A statistically significant decrease in average LES pressure from 38.23 mmHg (range 34.40–42.06 mmHg) before the procedure to 23.30 mmHg (range 20.79–25.81 mmHg) after botulinum toxin injection ($P < 0.01$) has been demonstrated[125]. Usually, botulinum toxin is injected into the four LES quadrants. Botulinum toxin injection can improve achalasia symptoms by decreasing LES pressure and improving oesophageal emptying[126], but the duration of benefit is short (median 6–9 months), necessitating repeated injection to maintain benefits. A systematic review and meta-analysis of 22 uncontrolled studies involving 730 patients with achalasia treated with botulinum toxin injection showed that therapeutic success, defined by an Eckardt score of ≤3, was achieved in 77% of patients during a follow-up period of 1–6 months[125]. Adverse events, including chest pain, heartburn and oesophageal perforation with mediastinitis, have been reported, but they are rare[127]. When successful, botulinum toxin injections can be offered to patients with other diseases that preclude other invasive management options.

Endoscopic and surgical therapy

Pneumatic dilation. Pneumatic dilation (PD) is an endoscopic procedure in which LES fibres are disrupted through pressurized distension of a stiff balloon centred across the LES, typically under fluoroscopic guidance. Graded balloons of 30 mm, 35 mm and 40 mm diameter are generally used, always starting with a 30 mm balloon to reduce the risk of perforation. Progression to a larger diameter is reasonable if response is suboptimal, and most patients tend to undergo a 30 mm followed by a 35 mm PD for sustained symptom response, which reduces the risk of perforation to 1%, compared with 9% if a 35 mm PD is performed initially[128]. In a systematic review and meta-analysis of 52 uncontrolled trials of PD in 4,166 patients with achalasia, clinical success (Eckardt score ≤3) was achieved in 83% of patients over a follow-up period of 3–6 months[125]. The rate of symptomatic GERD, the most common adverse effect of any intervention to disrupt the EGJ, was relatively low, occurring in 9% of the patients after 6 months. PD is a useful treatment option particularly in patients with type 2 achalasia, but also in those with type 1 achalasia; caution is needed when offering PD to patients younger than 40 years, with baseline chest pain, male sex, and those with basal LES pressures of >30 mmHg, as repeat procedures are often needed[129]. It is particularly useful in patients who present with recurrent symptoms after one of the other treatment modalities, especially in regions without access to advanced endoscopic skills, such as those required for POEM (FIG. 5).

Per-oral endoscopic myotomy. POEM is an innovative technique that has gained popularity since its first description in 2007 as an effective and safe treatment modality in achalasia. During upper endoscopy under sedation, a mucosal incision is created in the middle to distal oesophagus, and the endoscope is advanced within the oesophageal submucosal layer using blunt dissection[130]. A tailored myotomy of the oesophageal and LES circular muscle is performed using a cautery device, and the mucosal incision is subsequently closed using endoscopic clips. The length of myotomy can be tailored to the individual's unique motor pattern and can be extended from the upper oesophagus to the proximal stomach, which is particularly relevant with pan-oesophageal spastic contractions in achalasia type 3 where a long myotomy is preferred, in contrast to achalasia types 1 and 2 where a short myotomy can suffice[131,132].

POEM results in a significant reduction in LES pressure with associated improvement in dysphagia symptoms, and an efficacy of 82–98% over a follow-up of 3 months to 3 years[133]. In a large series of 500 patients with achalasia treated between 2008 and 2013, the mean Eckardt score decreased from 6 to 1; however, 21.3% of patients developed GERD manifestations at the 3-year time point[134]. In a meta-analysis of 36 studies with a total of 2,373 patients, 98% of procedures were considered successful with reduction in Eckardt score to ≤3. By contrast, abnormal oesophageal acid exposure on pH testing was observed in 47%, suggesting a high rate of GERD after POEM[135].

Although no long-term follow-up data from randomized controlled trials are yet available, several cohort studies have demonstrated that POEM can be effective even after 10 years of follow-up[136]. Although higher grades of reflux oesophagitis are uncommon after POEM[137], one study reported moderate-to-severe oesophagitis in 40% of patients with GERD symptoms, and endoscopic oesophagitis even in those without symptoms[138]. Caution should be adopted in evaluating young patients, as POEM may expose them to lifelong reflux with potential for peptic strictures, Barrett oesophagus and even oesophageal cancer.

Laparoscopic Heller myotomy. Heller myotomy was introduced as an open surgery more than a century ago, but the procedure has evolved to laparoscopic Heller myotomy (LHM), which comprises an anterior cardiomyotomy that disrupts both circular and longitudinal muscle fibres up to 5–7 cm proximally from the EGJ and at least 2 cm onto the gastric cardia[139]. Robotically assisted Heller myotomy has also been described, but systematic review and meta-analysis has not shown any significant advantage over the laparoscopic approach with the exception of a decrease in the rate of intraoperative oesophageal perforation[140]. Of note, a partial anterior or partial posterior fundoplication is routinely performed as part of LHM, primarily because a randomized controlled study found objective reflux in 48% of patients without a fundoplication compared with 9% with a partial fundoplication at LHM after 3–5 months of follow-up[141]. There does not seem to be any significant difference in long-term outcomes for dysphagia and reflux, provided the fundoplication is partial and not total[142]. LHM has excellent efficacy, with an improvement in symptom scores in >90% and high satisfaction in >90% of patients for up to 5 years after the procedure[139,143].

The procedure has a high safety profile in carefully selected patients. Potential complications include mucosal perforation, splenic injury, pneumothorax and incisional bleeding. A large single-centre series of 400 patients reported morbidity and mortality rates of 2% and 0%, respectively, and an initial failure rate of 10%[144]. In a long-term follow-up study, satisfaction rates decreased to 75% at 15 years, owing to both dysphagia and reflux, even though pathological reflux was documented objectively in only 14% of 149 patients[143]. Similarly, erosive oesophagitis was seen on endoscopy in only 25% during a 5-year follow-up period after LHM with partial fundoplication[145].

Comparison of procedures. Various therapeutic options with high levels of clinical efficacy are now available for achalasia management, which makes selection of the optimal approach difficult. Thus, several comparative studies have been published in the past decade to help prioritize management options.

A single series of PD procedures is as effective as LHM in relieving symptoms at 1-year follow-up[146], but less effective than POEM[147], without differences in safety or risk between the options. In studies in which PD was repeated owing to symptom recurrence, efficacy and safety between PD and LHM were similar[129]. In the past 3 years, hydraulic dilation using a stiff 30 mm dilating balloon in conjunction with FLIP has been used as an alternative to PD without the need for fluoroscopy, with comparable symptomatic outcomes in retrospective and open label studies[148,149]. However, a 35 mm dilating balloon is not available using this approach, and randomized comparisons with PD have not been performed.

No long-term follow-up data from randomized controlled trials are available yet, but POEM seems to be as effective as LHM as a first-time treatment of patients with achalasia[120,150]. In 2019, a randomized trial showed that POEM was non-inferior to LHM with Dor fundoplication in controlling achalasia symptoms at 2 years, but GERD was more common in patients who underwent POEM than in those who underwent LHM[151]. By contrast, another randomized clinical trial found that treatment success was significantly better with POEM than with PD (95% versus 54%, respectively) after a 2-year follow-up period[147]. POEM is particularly effective in type 3 achalasia (FIG. 5), which is associated with a higher likelihood of treatment failure of botulinum toxin injections, PD and LHM than type 2 achalasia[120,152,153]. A multicentre retrospective cohort study of 75 patients with type 3 achalasia demonstrated a higher clinical response rate with POEM (98%) than with LHM (81%, $P = 0.01$), reflecting the longer tailored myotomy length possible with POEM[154]. Thus, POEM is a safe and effective therapy for achalasia, with infrequent serious adverse events. Of note, GERD is a more frequent adverse effect after POEM than after LHM or PD[120].

LHM achieves similar achalasia-related symptomatic control to PD and POEM in type 2 achalasia, and is the preferred approach in type 1 achalasia, as it performs particularly well in patients with pre-treatment LES pressures >30 mmHg (REF.[155]).

Salvage therapy with symptom recurrence. As none of the treatment options for achalasia is uniformly effective, and the underlying motility disorder is not curable, salvage therapy is often required when symptoms recur. Objective evaluation of symptom recurrence can include endoscopy, HRM, TBE or FLIP; symptom assessment alone, even with use of validated measures such as the Eckardt score may not provide enough data to recommend repeat invasive management. PD has been demonstrated to be safe after LHM failure in a systematic review involving 87 patients with failed LHM, with a success rate of 89%[156]. Limited available data suggest safety and efficacy of PD following POEM as well[157]. Case series exist in which patients with failed PD and POEM have been managed successfully with LHM[157,158], which can be offered before oesophagectomy even when a sigmoid oesophagus is encountered in these failures[159]. Finally, POEM is emerging as a safe and effective option after failure of LHM, with 94% efficacy in a multicentre case series[160]. Small case series also document improvement of barium column height and symptoms after POEM following failed PD[161,162]. Thus, any of the other two options is feasible when achalasia symptoms persist or recur despite LHM, PD or POEM, but the available literature does not provide guidance on the optimal option in each clinical setting.

End-stage achalasia and oesophagectomy

Despite adequate disruption of the LES, achalasia progresses to end-stage disease in ~5% of patients, which is characterized by a dilated (>6 cm) and tortuous sigmoid oesophagus on barium swallow[163,164]. A key consequence is the formation of a 'sump' in the lower oesophagus, leading to pooling of food and fluid. End-stage achalasia can lead to considerable morbidity, including malnutrition, aspiration and pulmonary complications such as pneumonia, and chronic severe oesophagitis[165]. International guidelines suggest trialling all invasive options (PD, POEM, LHM) in end-stage achalasia[166], but an oesophagectomy with gastric pull-up or colonic interposition may be indicated in patients who are candidates for surgical removal of the dilated, functionless oesophagus[2]. Morbidity and mortality with oesophagectomy are high at 50% and 0.9%, respectively[166–168]. Enteral feeding to bypass the oesophagus is an option for patients unfit for oesophagectomy[2].

Quality of life

Symptom questionnaires

Standardized questionnaires are helpful to assess symptom severity, symptom response to therapy and quality of life in achalasia. The Eckardt score is a 4-item self-report scale that is easy to use, with short, simple questions, evaluating the most common achalasia symptoms[169]. Each of dysphagia, regurgitation, chest pain and weight loss is graded from 0 to 3, with a maximum possible score of 12 (TABLE 1). The Eckardt score was initially developed to assess efficacy of achalasia management, with a post-treatment score ≤3 being considered optimal. The score demonstrates fair reliability and validity[170], mainly from questions on dysphagia and regurgitation. However several limitations exist,

Box 2 | **Experience of an anonymous patient with severe achalasia**

During my adolescence in 1996, I was struck with the inability to eat. It felt like food was stuck in my chest beating a drum vigorously, a sensation that I could not quiet or stop. When I tried to swallow a morsel of food, pain radiated in my chest for 30 minutes. My condition worsened when I started experiencing severe chest spasms without eating that were mistaken for heart attacks. After several normal endoscopies and taking ineffective medication for acid reflux, I was told all symptoms were psychosomatic. Months later, following barium studies and manometry, I was diagnosed with achalasia, a rare disease with no known cause or cure. Watching everyone around me eat, feeling the pangs of hunger, feeling like an alien is going to pop out of my chest at any moment, my teenage years became a boot camp for how to conceal pain.

Various treatments were unsuccessful, including oesophageal botulinum toxin injections and pneumatic dilations. On a liquid diet, my weight decreased and I constantly managed alienating pain. My first open surgery in 1997, a Heller myotomy, failed. The second myotomy succeeded insofar that I could eat again. The chest spasms, my greatest foe, persisted. I carried in me an indiscriminate ticking time bomb that exploded often and in any situation imaginable (driving, flying, hiking). I was prescribed psychotropic medication for oesophageal hypersensitivity. When medication and water failed to temporarily calm my symptoms, I routinely visited the emergency room. In my wallet, I carried a letter from my doctor explaining what achalasia is to help other physicians treat me. At this point, I had normalized the 'near-death' experience.

In the mid-2000s, eating became more arduous again. My oesophagus was enlarging, becoming S-shaped, like a flat tyre folding on itself. Drinking 3.5 litres of water was necessary to push a meal down my uncooperative, winding oesophagus. In 2012, I faced the inevitable, an oesophagectomy. I have lived two lives: one with an oesophagus and one without. The latter has been easier. My relationship with food remains complicated, but I can eat and the chest spasms have been vanquished. I can't lay flat on my back or stomach, my chest burns when I reach down to tie my shoes, I don't love eating in public (especially in nice restaurants with small cups for water), splitting the bill at a tapas restaurant is laughably against my favour, I get passive-aggressive looks when I turn down food at social gatherings, but all of this barely registers in me because life with an oesophagus was a nightmare, as if I was alone in space and no one could hear me scream.

mainly because diet restriction and food avoidance could lead to reduced scores in patients who restrict eating to lessen symptoms, which can explain the suboptimal reliability observed in some studies[170,171]. The Eckardt score is also limited by a recall period, by equal weighting of all symptoms and by a lack of psychometrically validated cut-off thresholds for success or failure. Other dysphagia scores used in achalasia include the Achalasia Severity Score[146], Vantrappen Dysphagia Score[172] and Watson Dysphagia Score[173], but the simplicity of the Eckardt score makes it popular despite its limitations.

The Brief Oesophageal Dysphagia Questionnaire (BEDQ) explores frequency and severity of dysphagia for food of various consistencies (liquid, solid, soft) on 5-point Likert scales addressing six items during the previous 14 days[174]. Two items measure the frequency of pain and coughing during swallowing in the previous 14 days, again on 5-point Likert scales. The final two items evaluate the number of food impactions lasting longer than 30 min and the number of emergency department visits over the previous year. The BEDQ is a rapid, reliable and validated tool to assess oesophageal dysphagia regardless of the underlying mechanism. The BEDQ may also be more sensitive than the Eckardt score for manometric diagnoses[175]. Although the BEDQ is more precise than the Eckardt score in assessing dysphagia, the Eckardt score is more inclusive, as it assesses regurgitation, chest pain and weight loss, which are important achalasia symptoms.

Quality of life

Achalasia symptoms negatively affect eating, quality of life and productivity (BOX 2). Owing to the substantial effects on eating function, patients with achalasia can be misdiagnosed with anorexia nervosa with or without bulimia[176]. Anxiety and hypervigilance can be predictors of dysphagia severity in patients with oesophageal motility disorders[177]. Similarly, depression is a frequent comorbidity in achalasia owing to the impairment of quality of life[178]. Thus, in addition to individual symptoms, measuring quality of life is important to guide treatment and evaluate treatment response in achalasia.

A 10-item achalasia-specific quality of life questionnaire (ASQ) measures disease-specific health-related quality of life taking into account food tolerance, dysphagia-related behaviour modifications, pain, heartburn, distress, lifestyle limitation and satisfaction[78]. ASQ scores demonstrate that quality of life correlates poorly with objective testing in achalasia[179], indicating that quality of life assessments are complementary to objective tests and need to be considered when planning management. Management of achalasia improves quality of life[180,181], but a diagnosis of achalasia in childhood is associated with continued impairment of quality of life into adulthood[182].

Prognosis

Morbidity and mortality in achalasia, and consequently the prognosis, are influenced by the complications of the disease. Before the institution of effective treatment, half of the patients with achalasia are at risk of malnutrition regardless of their weight[183]. Compared with the general population, there is an increased risk of aspiration pneumonia (incidence rate ratio (IRR) 13.38, 95% CI 1.66–107.79), lower respiratory tract infection (IRR 1.33, 95% CI 1.05–1.70), oesophageal malignancy (IRR 5.22, 95% CI 1.88–14.45) and mortality (IRR 1.33 95% CI 1.17–1.51)[16].

The risk of oesophageal malignancy is hypothesized to be related to two factors. The first is poor oesophageal clearance that promotes bacterial growth, chemical irritation and mucosal inflammation leading to dysplastic changes and development of squamous cell carcinoma[184]. Additionally, increased oesophageal acid exposure after achalasia treatment can lead to Barrett mucosa and oesophageal adenocarcinoma[185]. However, the exact risk of oesophageal malignancy is not fully known, partly because of differences in study design and setting[186]. Although the absolute risk of oesophageal cancer is low, the risk ratio of squamous cell carcinoma is estimated to be 72 times, and that of oesophageal adenocarcinoma six times higher than that in the general population[185–188]. Most malignancies are observed more than 10 years after achalasia diagnosis. Male sex and Chagas disease are known to confer an increased risk of malignancy, and the type of treatment and number of re-interventions continue to be debated as potential risk factors[189,190]. Finally, the increased mortality in patients with achalasia reported by some studies[16,17] remains controversial, as other studies did not find differences in causes of death and life expectancy compared with the general population[18,165].

Box 3 | **Areas in need of further research**

- Improved understanding of achalasia pathogenesis
- Detailed study of oesophageal biopsy, serum, DNA and RNA samples
- Suitable animal model of achalasia
- Development of modern patient-reported outcome (PRO) questionnaire
- Predictors of non-response to initial treatment
- Assessment of treatment response in childhood achalasia
- Improved objective evaluation of treatment response using modern tools
- Evaluation of long-term consequences of per-oral endoscopic myotomy
- Screening and surveillance for dysplasia and cancer

Outlook

In view of the rarity of the condition, an international and multicentre approach is essential for advancing our understanding of achalasia[14–17] (BOX 3). In the past decade, several international multicentre trials have established considerable efficacy of diverse available treatment modalities[129,147]. Nevertheless, unanswered questions remain, which will also require multicentre approaches. A better understanding of the pathogenesis and predisposition for achalasia, and evaluation of novel treatment approaches, such as variants of POEM and robotically assisted oesophagocardiomyotomy, are needed[120,166].

The pathogenesis of achalasia remains poorly understood. Evidence for genetic predisposition and immune-mediated destruction of myenteric neurons, possibly triggered by a viral infection, exists, but a detailed understanding of disease triggers, insights into mechanisms and pathways, and a suitable animal model are all lacking[191]. A large-scale collection of biological samples from patients with achalasia at different stages of the disease is required to enhance our understanding, including serum and DNA samples and neuromuscular biopsy specimens obtained during POEM or LHM. Studying biopsy specimens will be crucial to evaluate the presence of viral material and to characterize involved immune cell subtypes and their roles. Pathways that are activated near the myenteric plexus can be studied using bulk RNA sequencing, cytokine and other immune signalling mediator expression assessment and more-targeted single-cell RNA sequencing. These insights are essential before immune-targeted or neuronal stem cell approaches can be considered for managing achalasia early in the disease and in the long term.

The primary outcome variable for evaluation of achalasia treatment efficacy in all recent trials is symptom based, using the Eckardt score[129,147]. This long-established score was not developed or validated according to current standards for PRO generation, and there is a clear need to develop a modern PRO questionnaire for achalasia, for application in future trials. This process is probably best coordinated through an international scientific organization. Moreover, as the relationship between symptoms and objective measures of achalasia status (manometry, TBE, FLIP measurements, oesophageal diameter and length) is highly variable, future definitions of clinical response or success will preferably be based on a combination of PRO and objective measures. A validated ASQ for achalasia is already available[78].

Although recent controlled trials showed high success rates and low rates of adverse events in short-term and medium-term evaluation, management of patients who do not respond to initial therapy remains a challenge[129,147]. An increasingly common trend, especially in centres with expertise in all therapeutic modalities for achalasia, is the establishment of a benign oesophageal motility multidisciplinary team (MDT) to discuss complex cases[192]. Analyses of the currently available data have failed to establish reliable predictors of non-responsiveness to available treatments, and future international cohort studies will need to study objective measures from HRM, TBE and novel approaches, such as FLIP, to establish clinically evaluable predictors of (poor) outcome. There is a relative paucity of outcome data in type 3 achalasia, which seems to be less responsive to PD, especially in paediatric populations. Both childhood and adult achalasia groups will benefit from international cohort studies, with or without a predefined treatment strategy (for example, surgical myotomy compared with POEM in type 3 achalasia).

Achalasia is a lifelong disease and, therefore, long-term follow-up data are needed, especially when considering cancer risk of incompletely resolved achalasia and risk of GERD and its complications from POEM. The controlled clinical trials already preformed as well as new prospective cohort series need to aim for follow-up periods beyond the range of 5 years[129,147], which may also elucidate areas with lack of clarity or consensus in existing guidelines, such as the utility of endoscopic surveillance for the detection of squamous carcinoma[120,166]. The increasing use of POEM generates a large population of patients at risk of GERD and its complications, including Barrett oesophagus and adenocarcinoma, which could justify endoscopic follow-up assessments in their own right. Finally, one of the long-term treatment goals of achalasia is the prevention of deterioration to a dilated and tortuous oesophagus. For all these reasons, endoscopic interval follow-up could be needed, but needs to be supported with evidence. Prospective studies can add image enhancement for detection of squamous carcinoma and FLIP or other techniques to quantify oesophageal diameter, enabling identification of the achalasia population with the highest screening yield and the appropriate screening interval. Specifically for POEM, the role of maintenance proton pump inhibitor therapy and the risk of developing oesophagitis, strictures or Barrett oesophagus needs prospective follow-up data[193].

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Introduction (E.S., C.P.G. and S.B.); Epidemiology (S.R.); Mechanisms/pathophysiology (D.S.); Diagnosis/screening/prevention (C.P.G.); Management (E.S. and S.K.T.); Quality of life (S.R.); Outlook (J.T.); Overview of the Primer (E.S.).

Competing interests
E.S. has served as speaker for AbbVie, AGPharma, Alfasigma, EG Stada Group, Fresenius Kabi, Grifols, Janssen, Innovamedica, Malesci, Medtronic, Novartis, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda and Unifarco; has served as consultant for Alfasigma, Amgen, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Falk, Fresenius Kabi, Janssen, Merck & Co., Reckitt Benckiser, Regeneron, Sanofi, Shire, SILA, Sofar, Synformulas GmbH, Takeda and Unifarco; and has received research support from Reckitt Benckiser, SILA, Sofar and Unifarco. S.B. has served as speaker for Medtronic. S.R. has served as consultant for Reckitt Benckiser and Dr Falk Pharma; and has received research support from Medtronic and Diversatek Healthcare. D.S. has served as consultant for Reckitt Benckiser UK, Jinshan Technology China and Alfasigma Italy. J.T. has served on the speaker bureau for Abbott, Mylan and Takeda; has served as consultant for Arena, Bayer, Falk, Takeda and Truvion pharmaceuticals; and has received research support from Shire, Sofar and Takeda. S.K.T. has served as a consultant for Medtronic. C.P.G. has served as speaker for Medtronic, Takeda and Johnson&Johnson, and has served as consultant for Medtronic, Diversatek, Takeda and Ironwood.

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