Achalasia

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Achalasia is a rare motility disorder of the oesophagus characterised by loss of enteric neurons leading to absence of peristalsis and impaired relaxation of the lower oesophageal sphincter. Although its cause remains largely unknown, ganglionitis resulting from an aberrant immune response triggered by a viral infection has been proposed to underlie the loss of oesophageal neurons, particularly in genetically susceptible individuals. The subsequent stasis of ingested food not only leads to symptoms of dysphagia, regurgitation, chest pain, and weight loss, but also results in an increased risk of oesophageal carcinoma. At present, pneumatic dilatation and Heller myotomy combined with an anti-reflux procedure are the treatments of choice and have comparable success rates. Per-oral endoscopic myotomy has recently been introduced as a new minimally invasive treatment for achalasia, but there have not yet been any randomised clinical trials comparing this option with pneumatic dilatation and Heller myotomy.

Introduction

Achalasia is a motility disorder of the oesophagus that presents with symptoms of dysphagia, regurgitation of undigested food, respiratory symptoms (nocturnal cough, recurrent aspiration, and pneumonia), chest pain, and weight loss.[1,2] Since its first description in 1674 by Sir Thomas Willis,[3] spasm or failure to relax the lower oesophageal sphincter (LOS) has been identified as the cause of achalasia, resulting in impaired flow of ingested food into the stomach and subsequent stasis of food and secretions in the oesophagus. Achalasia results from the disappearance of the myenteric neurons that coordinate oesophageal peristalsis and LOS relaxation.[4]

The most common form of achalasia is idiopathic achalasia, which mostly occurs as sporadic cases. However, a similar clinical presentation can occur in patients with pseudoachalasia (2–4% of patients with suspected achalasia)[5] or Chagas disease—diseases characterised by degeneration of the myenteric plexus due to neoplastic infiltration[6,7] or infection with *Trypanosoma cruzi,* respectively.[8–10] Moreover, sporadic cases of paraneoplastic pseudoachalasia associated with anti-Hu antibodies have been reported, especially in patients with small-cell lung cancer.[11] Although rare, achalasia can also be part of other complex syndromes such as Allgrove syndrome (also known as triple A syndrome—ie, alacrima, achalasia, adrenocorticotropic hormone deficiency), Down's syndrome, or familial visceral neuropathy.[12] In this Seminar, we mainly focus on the present insights and recent developments in the management of idiopathic achalasia.

Epidemiology

Idiopathic achalasia is rare, with mean incidences of 0·3–1·63 per 100 000 people per year in adults[13–16] and 0·18 per 100 000 people per year in children younger than 16 years.[17] In adults, achalasia occurs with equal frequency in men and women[14,15] and in white and non-white people,[18] but incidence increases with age. In most studies, the mean age at diagnosis was over 50 years.[13,14,18] Mean incidence in those aged over 80 years is 17 per 100 000 people per year (95% CI 2–61).[13] Mean prevalence was 8·7 per 100 000 people in a study from Iceland[15] whereas it was 10·8 per 100 000 people in a Canadian population-based study.[14] In both studies, the prevalence increased over time whereas the incidence remained constant, most likely because achalasia is a chronic disorder with a low disease-related mortality rate. In an attempt to identify potential causative or environmental factors, Farrukh and colleagues[13] studied the epidemiology of achalasia in the immigrant south Asian population in Leicester (UK). Over 20 years, no changes in frequency of achalasia were reported, arguing against potential environmental factors as triggers of the disease. The finding that autoimmune diseases such as type 1 diabetes mellitus, hypothyroidism, Sjögren's syndrome, and uveitis are more prevalent in patients with achalasia than in the general population suggests that achalasia might have an autoimmune component.[19]

Pathophysiology

Immune-mediated ganglionitis

Oesophageal peristalsis and relaxation of the LOS are mediated and coordinated by myenteric neurons.[4] In achalasia, these myenteric neurons are decreased in number or are absent, resulting in aperistalsis and impaired relaxation of the LOS. Most likely, the myenteric neurons disappear because of chronic ganglionitis. Detailed examination of resection specimens shows infiltration of cytotoxic lymphocytes expressing activation markers[20–22] and evidence of complement activation within myenteric ganglia.[23] In accordance, antibodies against myenteric neurons have been shown in serum samples of patients with achalasia,[24,25] especially in those

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Search strategy and selection criteria.

We searched PubMed and the Cochrane library with no date limits set for medical subject heading terms achalasia", "epidemiology", "etiology", "pathophysiology", "genetics", "diagnosis", "manometry", "radiology", "symptoms", "endoscopy", "treatment", "pharmacological", "botulinum toxin", "pneumodilation", "myotomy", "POEM", "end-stage", "dysplasia", "carcinoma", and "stem cells". We did the last search in January, 2013. We reviewed all relevant articles published in English. For treatment strategy, we regarded randomised trials and meta-analyses as the most important study types. Where appropriate, we reviewed relevant abstracts presented at major gastrointestinal meetings.

with HLA DQA1*0103 and DQB1*0603 alleles.[26] Because HLA proteins are crucial for antigen recognition, these findings suggest the involvement of an aberrant immune response to so far unknown antigens. Viruses, such as herpes simplex virus 1 (HSV-1), measles, and human papillomavirus have been proposed as potential antigens. HSV-1 DNA has been identified in oesophageal tissue, and evidence suggests that isolated oesophageal T cells are oligoclonal in nature in achalasia and specifically proliferate and release cytokines on exposure of HSV-1 antigens.[27,28] Because HSV-1 is a neurotropic virus with a

predilection for squamous epithelium, this hypothesis would fit with the selective loss of enteric neurons in the oesophagus. However, HSV-1 DNA was as frequently identified in the oesophagus of control individuals,[28] suggesting that HSV-1 only triggers persistent immune activation with subsequent loss of enteric neurons in genetically susceptible individuals (figure 1).[29] However, other investigators have not found HSV-1 or other viruses such as measles or human papillomavirus in oesophageal resection specimens from patients with achalasia.[22,30,31]

Genetics

Candidate gene studies, albeit in a small number of patients, have identified an association between achalasia and gene polymorphisms in HLA class II molecules,[32–34] vasoactive intestinal peptide receptor 1,[35] KIT,[36] interleukin 10 promoter,[37] and interleukin 23 receptor.[38] Moreover, familial achalasia has been reported, albeit rarely, further supporting a role for genetic factors in the pathogenesis of achalasia.[12] An ongoing genome-wide association study will hopefully yield more clarity regarding this topic.

Diagnosis

Symptomatology

The most frequently occurring symptoms of achalasia are dysphagia (>90%) for solids and liquids, regurgitation of undigested food (76–91%), respiratory complications (nocturnal cough [30%] and aspiration [8%]), chest pain (25–64%), heartburn (18–52%), and weight loss (35–91%).[1,39–41] Heartburn can lead to an erroneous diagnosis of gastro-oesophageal reflux disease, which might culminate in antireflux surgery. Nocturnal coughing mainly occurs in patients with substantial stasis of large amounts of food and secretions. Chest pain is predominantly present in patients with type III disease (see later)[42] and responds less well to treatment than do dysphagia and regurgitation, which probably explains the less favourable therapeutic results obtained in patients with type III disease compared with those with type I or II disease.[40,42] However, symptoms of achalasia are not specific, which explains the long delay between onset of symptoms and the final diagnosis (up to 5 years in some studies).[43,44] Although some patients lose a lot of weight (more than 20 kg),[1] achalasia should also be considered in obese patients.

Radiology and endoscopy

The first diagnostic step is to rule out anatomical lesions, neoplasia, or pseudoachalasia using endoscopy or radiology. Pseudoachalasia should particularly be suspected in cases of rapidly progressing dysphagia, significant weight loss, and old age,[6] and should be excluded by endoscopic ultrasound or CT scan. These investigations will reveal unusual thickening of the oesophageal wall, mass lesions, or even an infiltrating pancreatic carcinoma.[7]
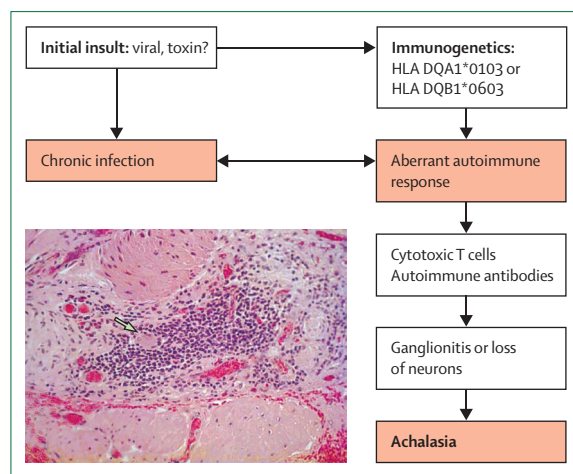

Figure 1: Present hypothesis proposing virus-induced autoimmune-mediated ganglionitis in achalasia
Insert shows infiltration of myenteric ganglion with T cells. Arrow shows myenteric nerves and ganglion cells. Reproduced with permission from Goldblum and colleagues.[21]
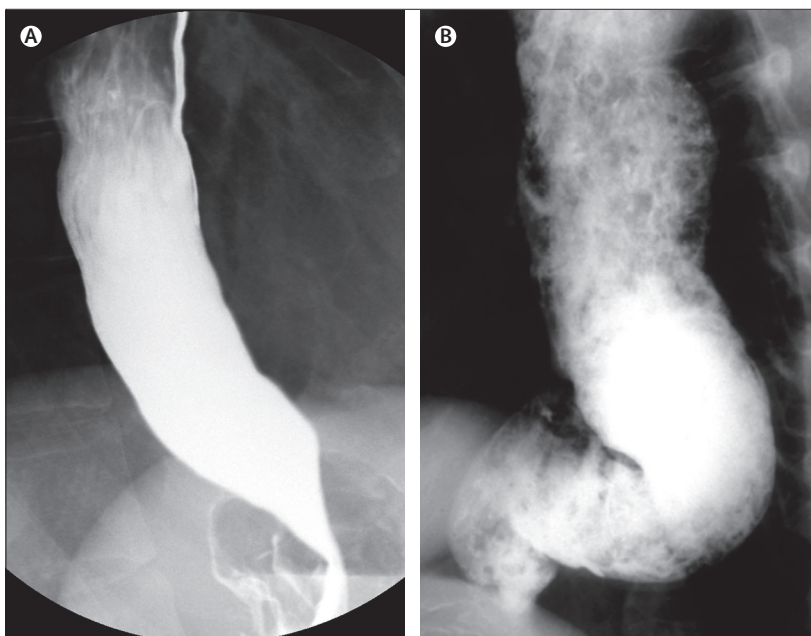

Figure 2: Achalasia findings on radiological examination
(A) Typical bird-beak appearance in early achalasia. (B) Sigmoid-like appearance of decompensated oesophagus. Modified from Moonen and Boeckxstaens[47] and Triadafilopoulos and colleagues,[48] respectively, with permission.

Especially in the early stage of achalasia, both endoscopy and radiology are less sensitive than manometry and only identify about half (or even less) of patients with early-stage achalasia.[41,45,46] In advanced cases, endoscopy might reveal a dilated oesophagus with retained food and increased resistance at the gastro-oesophageal junction. Radiological examination often shows a typical bird-beak image at the junction (figure 2), with a dilated oesophageal body, sometimes with an air–fluid level and absence of an intragastric air bubble. In more advanced achalasia, severe dilatation with stasis of food and a sigmoid-like appearance can occur. Although radiology is not as sensitive as manometry, this investigation remains important to rule out structural abnormalities, estimate the diameter of the oesophagus, and assess the presence of epiphrenic diverticula.[48] To assess emptying of the oesophagus, a timed barium swallow can be done, in which the height of the barium column 5 min after ingestion of diluted barium is a measure of emptying.[49,50]

Manometry

On conventional manometry, absence of peristalsis, sometimes with increased intraoesophageal pressure owing to stasis of food and saliva, and incomplete relaxation of the LOS on deglutition (residual pressure >10 mm Hg) are the hallmarks of achalasia.[2] Additionally, the resting tone of the LOS is often raised. High-resolution manometry (HRM) is increasingly being used to provide more detailed information on oesophageal motility.[51] By means of catheters incorporating 36 or more pressure sensors spaced only 1 cm apart, HRM allows detailed pressure recording from the pharynx to the stomach and is regarded as the gold standard for diagnosis of achalasia.[52] The use of HRM has led to the subclassification of achalasia into three clinically relevant groups on the basis of the pattern of contractility in the oesophageal body:[53] type I (classical achalasia; no evidence of pressurisation), type II (achalasia with compression or compartmentalisation in the distal oesophagus >30 mm Hg), and type III (two or more spastic contractions; figure 3). Additionally, a

new parameter to quantify LOS relaxation has been introduced: integrated relaxation pressure,[55] which calculates the mean post-swallow LOS pressure of a 4-s period during which the LOS pressure was lowest, skipping periods of crural contractions if necessary. The upper limit of normal for the integrated relaxation pressure is 10 mm Hg for type I achalasia, 15 mm Hg for type II achalasia, and 17 mm Hg for type III achalasia, which differentiates best the impaired relaxation in achalasia from non-achalasic individuals and from patients with diffuse oesophageal spasm.[56]

Treatment
Pharmacological compounds

The two most often used pharmacological drugs are nitrates and calcium-channel blockers.[57–60] Nitrates inhibit normal LOS contraction by dephosphorylation of the myosin light chain. In a Cochrane review, Wen and colleagues[61] identified only two (poorly designed) randomised studies that assessed the clinical success of nitrates in achalasia and concluded that no solid recommendations could be given. Nifedipine, in sublingual doses of 10–20 mg 15–60 min before meals, is the most widely used drug for achalasia. It inhibits LOS muscle contraction by blocking cellular calcium uptake and lowers the LOS resting pressure by 30–60%.[57–59] However, a substantial drawback of its use is the occurrence of side-effects such as hypotension, headache, and dizziness in up to 30% of patients.[57–59] Moreover, drug tolerance develops with time.[62]

A more widely used pharmacological treatment is botulinum toxin A, a neurotoxin that blocks the release of acetylcholine from the nerve terminals. It is directly injected, at a dose of 80–100 units in four or eight quadrants, into the LOS through a sclerotherapy needle during upper-gastrointestinal endoscopy.[63,64] Botulinum toxin is a safe and effective treatment with few side-effects. More than 80% of cases have a clinical response by 1 month, but response fades rapidly, with less than 60% of patients in remission at 1 year.[65] Findings from five
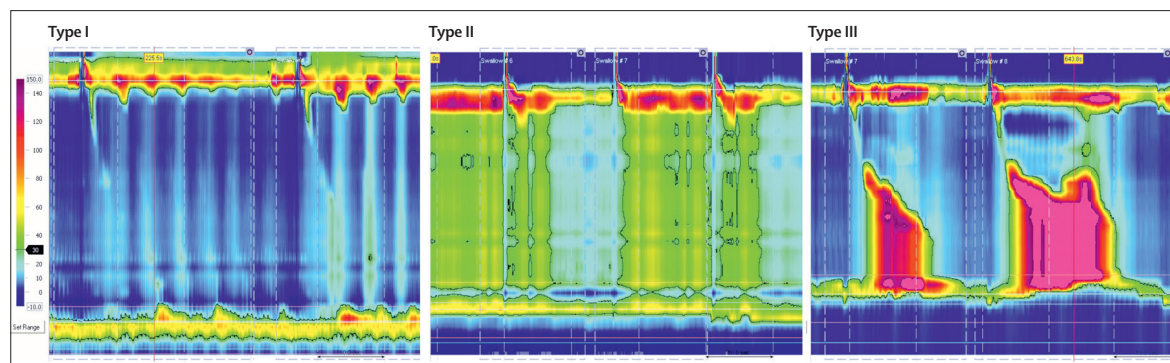

Figure 3: **Manometric types of achalasia**
Type I is characterised by absence of distal pressurisation to greater than 30 mm Hg. In type II, pressurisation to greater than 30 mm Hg occurs in at least two of ten test swallows, whereas patients with type III disease have spastic contractions with or without periods of compartmentalised pressurisation. Modified from Boeckxstaens and Zaninotto,[54] with permission.

randomised trials that compared botulinum toxin with pneumodilatation[66–70] and one that compared botulinum toxin with laparoscopic myotomy[71] showed initially comparable relief from dysphagia, but a rapid deterioration in patients treated with botulinum toxin after 6–12 months. Hence botulinum toxin, as is the case for nitrates and calcium-channel blockers, should be used only as an interim option before treatment with more durable treatments or in high-risk patients.

Pneumatic dilatation

Pneumatic dilatation, which tears the LOS by forceful stretching with air-filled balloons, has become simplified by the microinvasive Rigiflex balloon system (Boston Scientific, Marlborough, MA, USA). These non-compliant polyethylene balloons are available in three diameters (30, 35, and 40 mm), mounted on a flexible catheter placed over a guide wire at endoscopy. The general technique of pneumatic dilatation is summarised in the panel and figure 4, although the actual protocol varies across centres.[2] Under fluoroscopic guidance, the balloon is positioned across the LOS and gradually inflated until the waist is flattened. The most popular technique is a graded dilation protocol starting with a 30 mm balloon.[73] Subsequent dilations are spaced over 2–4-week intervals on the basis of symptom relief associated with repeat LOS pressure measurements[39,74] or improvement in oesophageal emptying.[75,76] Pneumatic dilatation is usually done in an outpatient setting; the patient is observed for 2–6 h and can return to normal activities the next day.

In a review of more than 1100 patients (24 studies) with an average follow-up of 37 months,[77] Rigiflex pneumatic dilatation resulted in good to excellent symptom relief in 74%, 86%, and 90% of patients treated with 30, 35, and 40 mm balloons, respectively. Over 4–6 years, nearly a third of patients have symptom relapse;[39,76,78] however, long-term remission can be achieved in nearly all these patients by repeat dilatation by an on-demand strategy on the basis of symptom recurrence.[78] Patients with the best outcomes after pneumatic dilatation are those older than 40 years, women, and those with a type II pattern by HRM.[1,42,49,53,76,79] The most cost-effective treatment for achalasia over a 5–10-year period after the procedure is pneumatic dilatation.[80,81]

Contraindications to pneumatic dilatation are poor cardiopulmonary status or other comorbid illnesses that would prevent surgery should an oesophageal perforation occur. Pneumatic dilatation can be done safely after a failed Heller myotomy, although larger diameter balloons are often needed.[82] Up to 33% of patients have procedure-related complications after pneumatic dilatation, but most are minor including chest pain, aspiration pneumonia, bleeding, transient fever, mucosal tear without perforation, and oesophageal haematoma. Oesophageal perforation is the most serious complication, with an overall rate in experienced endoscopists of 2·0% (range 0–16%), of which 50% needed surgery.[83] However, in a recent series of 16 transmural perforations, all cases were managed conservatively.[84] Small perforations and painful deep tears can be treated with antibiotics and total parenteral nutrition for days to weeks.[84] However, surgical repair by thoracotomy is best for large, symptomatic perforations with extensive soilage of the mediastinum. Most perforations occur during the initial dilatation; difficulty keeping the balloon in position is a potential risk factor.[85] Although no other predictors for perforation have been identified, a European achalasia trial reported more perforations, primarily in older patients, when the first pneumatic dilatation was done with a 35 mm compared with a 30 mm balloon.[79] Complications of severe gastro-oesophageal reflux disease are rare after pneumatic dilatation, but 15–35% of patients have heartburn, which improves with proton-pump inhibitors.[77]

Laparoscopic Heller myotomy

Surgical myotomy of the muscle layer of the distal oesophagus and LOS, also known as Heller myotomy, is a time-honoured treatment for achalasia. It was first described in 1913 by the German surgeon, Ernst Heller,[86] and has been widely used, with few technical changes, ever since. The two most important modifications to the original procedure are cutting of the cardia muscle fibres only on the anterior side[87] and addition of a fundoplication to reduce the risk of gastro-oesophageal reflux (figure 5).[90]

The advent of minimally invasive surgery has profoundly changed the approach to Heller myotomy. Pellegrini and colleagues[91] initially described a thoracoscopic approach for myotomy in 1992. However, laparoscopy offers better visualisation of the distal oesophageal muscle layers and the sling fibres of the gastric fundus,

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Panel: General techniques for pneumatic dilatation with the Rigiflex balloon system[2]

- Patients are on a liquid diet for several days and fast for 12 h before endoscopy. Those with mega-oesophagus might need oesophageal lavage with a large-bore tube.
- The procedure is usually done as outpatient surgery in the morning.
- Upper endoscopy with conscious sedation in the left lateral position is done.
- Savary guide wire is placed in the stomach and a Rigiflex balloon is passed over it.
- The smallest balloon (30 mm) is usually used first. Beginning with a 35 mm balloon might be preferred in patients with previous pneumatic dilatation failures, young patients (<40 years), or after previous Heller myotomy.
- Accurate balloon placement is usually done with fluoroscopy (sometimes endoscopy). The key is careful location of the balloon so the waist caused by the non-relaxing lower oesophageal sphincter impinges on the middle portion of the distending balloon.
- The balloon is gradually distended until the waist is flattened. The pressure needed is usually 7–15 psi of air, held for 15–60 s.
- The patient is repositioned in the left lateral position to minimise aspiration before the balloon is deflated and removed.
- Post-procedure observation is done for 2–6 h to exclude perforation and assess for chest pain and fever. Patients with significant pain should be sent for a Gastrografin swallowing assessment to exclude oesophageal perforation.

resulting in a shorter operation time and better results. In a recent review, Campos and colleagues[92] showed that symptomatic improvement was significantly better with laparoscopic (n=3086 patients) than with thoracoscopic (n=211 patients) Heller myotomy (89·3% vs 77·6%, odds ratio 1·9, 95% CI 1·1–3·7; p=0·048) and reduced the incidence of postoperative gastro-oesophageal reflux (14·9% vs 28·3%, odds ratio 2·8, 95% CI 1·1–7·2; p=0·03). Because the antireflux barrier function of the LOS is lost after myotomy, the need to add an antireflux procedure (fundoplication) to Heller myotomy has been debated for many years. Findings from the meta-analysis by Campos and colleagues[92] showed similar therapeutic success but a significant reduction of gastro-oesophageal reflux symptoms when a fundoplication was added to Heller myotomy (31·5% vs 8·8%; p=0·001). Similar results were reported in a randomised controlled trial.[93] In view of the absence of peristalsis in achalasia, the type of fundoplication applied might have a major effect on outcome. Postoperative dysphagia is higher after Nissen fundoplication than after partial anterior fundoplication (15·0% vs 2·8% p=0·001).[93,94] Findings from a recent multicentre trial suggest that both anterior (Dor) and posterior (Toupet) partial fundoplication provide comparable control of reflux after laparoscopic Heller myotomy.[95]

Laparoscopic Heller myotomy combined with partial fundoplication is a safe operation with a reported mortality of 0·1% (three deaths in 3086 patients).[92] The most common complication of laparoscopic Heller myotomy is perforation of the oesophageal or gastric mucosa during the myotomy, which is usually recognised during the procedure and repaired immediately without any consequences. The overall complication rate of laparoscopic Heller myotomy is 6·3% (range 0–35%), but clinical consequences are reported in only 0·7% (range 0–3%) of cases.[96–105] The table summarises the outcome data of studies with 100 patients or more.[96–105] In a systematic review, the mean success rate was 89% (range 76–100%) at a median follow-up of 35 months (range 8–38).[92] However, success rates decrease (depending on the definition used) to 65–85% at 5 years' follow-up, probably because of disease progression.[102,106,107]

Positive prognostic factors after laparoscopic Heller myotomy are young age (<40 years), a LOS resting pressure greater than 30 mm Hg, and a straight oesophagus (ie, with no tortuosities at its distal end, as in sigmoid oesophagus).[99,101] As for pneumodilatation, the manometric pattern at diagnosis also affects clinical success rates after Heller myotomy—ie, patients with achalasia type II have the best outcome.[108] Although no difference in outcome between Heller myotomy and pneumodilatation has been noted for patients with type I and II achalasia, patients with type III disease seem to respond better to Heller myotomy than to pneumodilatation,[42] probably because myotomy entails a more extensive and more proximal disruption of the oesophageal muscle than does dila-
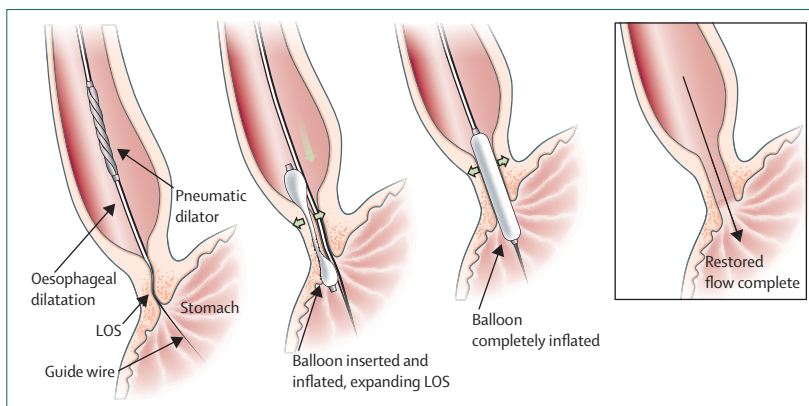

Figure 4: **Pneumatic dilatation with the Rigiflex system**
Schematic representation of the pneumodilatation procedure. The deflated balloon is inserted over a guide wire, after which the slightly inflated balloon is positioned at the oesophagogastric junction with the indentation still visible. Finally, the balloon is fully inflated and the indentation disappears. After removal of the balloon, the LOS is distended, allowing adequate passage. LOS=lower oesophageal splinter. Reproduced from Johns Hopkins Medicine, Gastroenterology and Hepatology.[72] Illustration Copyright ©1998–2003 by The Johns Hopkins Health System Corporation; used with permission www.hopkins-gi.org. Illustration created by Mike Linkinhoker.
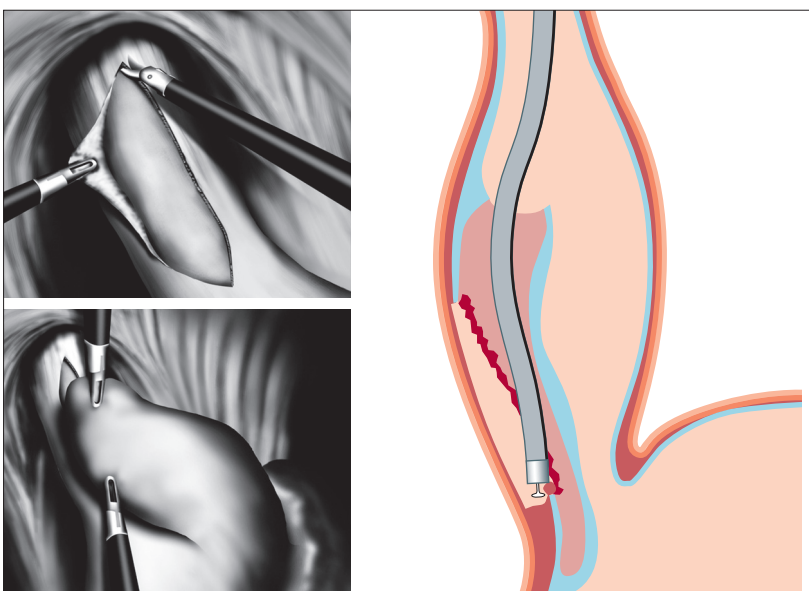

Figure 5: **Schematic representation of laparoscopic Heller myotomy with Dor fundoplication (left) and per-oral endoscopic myotomy (right)**
Left panels show the dissection of the muscle layer (top) and the creation of the Dor fundoplication (bottom). The right panel shows the endoscope positioned in the tunnel created between the muscle layer and mucosa, allowing endoscopic myotomy of the circular muscle layer. Reproduced from Zaninotto and Costantini[88] and Inoue and colleagues,[89] respectively, with permission.

tation.[108] The effect of past endoscopic treatment on the outcome of laparoscopic Heller myotomy is controversial: findings from some studies[102–104] suggested that multiple endoscopic treatments could hamper the results of surgery, whereas Portale and colleagues[109] reported that only patients previously treated with both botulinum toxin injection and pneumodilation had a less favourable outcome than did those who had not had such procedures previously. However, to what extent these patients are less responsive to any treatment remains unclear.

	Number of patients	Follow-up (months)	Patients in remission (%)
Oelschlager et al (2003)[96]	110	46	100 (91%)
Perrone et al (2004)[97]	100	26	92 (92%)
Rossetti et al (2005)[98]	195	83	179 (92%)
Torquati et al (2006)[99]	200	43	170 (85%)
Schuchert et al (2008)[100]	194	32	180 (93%)
Zaninotto et al (2008)[101]	400	30	348 (87%)
Snyder et al (2009)[102]	134	22	115 (86%)
Finley et al (2010)[103]	261	36	181 (69%)
Rosemurgy et al (2010)[104]	505	31	404 (80%)
Carter et al (2011)[105]	165	62	125 (76%)
Total	2264	42*	84%

*Mean.

Table: Remission of symptoms after laparoscopic myotomy in series of 100 or more patients

Recurrence of dysphagia most often develops within 12–18 months after surgery.[100,110] Incomplete myotomy, especially on the gastric side (where the myotomy is more difficult), late scarring of the myotomy, and an excessively tight anti-reflux wrap are possible causes of treatment failure.[110] As mentioned earlier, chest pain is more difficult to treat than the other symptoms and patients should be informed about this issue.[40] Recurrent symptoms after Heller myotomy can be safely treated with pneumodilatation or, if such conservative treatment fails, by repeat laparoscopic Heller myotomy.[110]

Pneumatic dilatation versus laparoscopic Heller myotomy

Until recently, addressing the question of whether to undertake pneumatic dilatation or laparoscopic Heller myotomy was difficult because large prospective, randomised comparative studies were not available. In a review of case series from 1989 to 2006, Campos and colleagues[92] reported an overall 68% improvement rate in 1065 patients undergoing pneumatic dilatation with Rigiflex balloons whereas laparoscopic myotomy had an 89% improvement rate in 3086 patients. In a study from the Cleveland Clinic (Cleveland, OH, USA),[76] 106 patients were treated with pneumatic dilatation and 73 patients underwent laparoscopic myotomy. Success, defined as dysphagia or regurgitation fewer than three times per week or freedom from alternative treatments, was similar between groups: 96% for dilatation versus 98% for surgery at 6 months, decreasing to 44% versus 57% at 6 years. A large retrospective longitudinal study from Ontario, Canada,[111] provides the best estimate of long-term outcomes with the procedures in typical practice settings. From 1991 to 2002, 1461 adults were treated for achalasia; 81% had pneumatic dilatation and 19% had surgical myotomy as their first procedure. The cumulative risk of any subsequent treatment (dilatation, myotomy, or oesophagectomy) after 1, 5, and 10 years was 36·8%, 56·2%, and 63·5% after initial pneumatic dilatation versus 16·4%, 30·3%, and 37·5% after initial

myotomy (hazard ratio 2·37; 95% CI 1·86–3·02). This risk difference occurred only when repeat pneumatic dilatation was recorded as an adverse event.

In 2011, a prospective randomised comparative study was published that compared pneumatic dilatation and laparoscopic myotomy undertaken by physicians highly skilled in both procedures.[79] In the European Achalasia Trial,[79] patients from five countries were randomly assigned to Rigiflex dilatation (n=94; 30 and 35 mm with up to three repeat dilations allowed) or laparoscopic myotomy with Dor fundoplication (n=106). Both treatments had comparable success in relieving symptoms at 2 years: 86% for dilatation and 90% for myotomy. Barium emptying and LOS pressure were both improved to similar extents in both groups. However, the follow-up was short (at least 2 years) and retreatment was allowed. Pre-existing daily chest pain, oesophageal width less than 4 cm before treatment, and post-treatment poor oesophageal emptying with barium column greater than 10 cm were identified as predictors of treatment failure. Although not a predictor of clinical success for either treatment, patients younger than 40 years more often needed repeat pneumatic dilatations than did those older than 40 years.

Per-oral endoscopic myotomy

Per-oral endoscopic myotomy (POEM) is a recently developed endoscopic technique for treatment of achalasia.[89] In brief, the endoscopist creates a submucosal tunnel to reach the LOS and to dissect the circular muscle fibres over a 7 cm oesophageal and 2 cm gastric length (figure 5). Inoue and colleagues[89] reported a success rate of 100% and a significant reduction in LOS pressure in 17 patients. Subsequent studies of 11–18 patients confirmed the high success rate (89–100%), even after several previous pneumatic dilatations.[112–116] However, physiological data are limited and follow-up was short (mean 6 months). Moreover, especially because no antireflux procedure is included in this technique, the risk of gastro-oesophageal reflux is substantial (up to 46% in one study[113]) and might represent an important drawback. Longer follow-up is needed and randomised studies to compare POEM with pneumatic dilatation or laparoscopic Heller myotomy should be done before accepting POEM as new treatment option for achalasia.

Oesophagectomy for end-stage achalasia

Despite the efficacy of pneumodilatation and laparoscopic Heller myotomy, 2–5% of patients will develop end-stage disease,[117] defined as a massive dilatation of the oesophagus with retention of food, unresponsive reflux disease, or the presence of preneoplastic lesions.[48] In these cases, oesophageal resection might be necessary to improve the patient's quality of life and avoid the risk of invasive carcinoma. The risk of needing oesophagectomy is higher if the oesophagus is already markedly dilated at the first intervention than if it is mildly dilated (<4 cm).[118]

The ideal reconstruction method after oesophagectomy has not yet been established. Gastric interposition has the advantage of needing only one anastomosis, but gastro-oesophageal reflux can cause severe damage if the anastomosis is intrathoracic. If a total oesophagectomy is done and the anastomosis is in the neck, the critical vascular supply to the gastric tube can be compromised, resulting in anastomotic leakage and stricture.[48] Alternatively, a long colonic interposition can be constructed, but anastomotic failure or stricture due to ischaemia might occur. Short-segment colon interposition with an intrathoracic anastomosis might be a valid option in such patients.[48] In a recent review that included 295 patients,[119] an optimum outcome (defined as unrestricted or regular diet) was present in 65–100% of patients at a medium follow-up of 44 months (range 25–72), irrespective of the technique used.

Risk factors and therapeutic guidelines

Standardisation of balloon systems and development of laparoscopic myotomy and, most recently, HRM has helped better define the types of patient who will respond well to pneumatic dilatation versus laparoscopic myotomy. These predictors are age, sex, and manometric type by HRM. The favourable effects of older age (>40 years) on the success of pneumatic dilatation are the most reproducible, from as far back as 1971.[1,74,76,79] Findings from several studies suggest that young men respond less well than do women to pneumatic dilatation.[76,120] For example, in a study at the Cleveland Clinic (106 patients, 51 women),[76] men up to age 50 years had poor outcomes after a 30 mm Rigiflex pneumatic dilatation. However, young women (<35 years) also did not respond well, whereas most women aged 35 years or older had sustained relief over at least 5 years after a pneumatic dilatation. Although not well studied, this finding is probably a result of stronger LOS tone in young patients, especially men.[121] Pandolfino and colleagues[53] reported that HRM patterns in achalasia predicted treatment success, especially after pneumatic dilatation. Success rates were significantly higher for type II achalasia (96%) than for type I (56%) and type III (29%) achalasia. These findings were supported by the prospective European Achalasia Trial, which reporting that type III disease might be best treated by laparoscopic myotomy.[42]

Identification of predictors of success can guide our recommendation for treatment of achalasia (figure 6).[2] Healthy patients with achalasia should be given the option of graded pneumatic dilatation or myotomy. Myotomy will be the more effective treatment in adolescents and younger adults, especially men and possibly patients with type III achalasia. Myotomy is also the treatment of choice in uncooperative patients and those in whom pseudo-achalasia cannot be excluded. Women and patients older than 40–50 years can expect good outcomes with either pneumatic dilatation or myotomy. Botulinum toxin injection should be the first-line treatment for elderly

patients or those with severe comorbid illnesses because it is safe, improves symptoms, and might need retreatment no more than yearly. However, pneumatic dilatation is a reasonable alternative in high-risk patients if done in high-volume (ie, experienced) centres with surgical expertise, should the rare perforation occur. The role of POEM as a substitute for myotomy will be defined in time once there has been longer term follow-up of symptoms and physiological studies.

Long-term management

To screen or not to screen for dysplasia?

As a result of functional obstruction, large amounts of food and saliva can be retained within the oesophagus, especially if treatment is suboptimal. Increased bacterial growth and chemical irritation from the continuous decomposition of food and saliva can induce chronic hyperplastic oesophagitis, dysplasia, and eventually malignant transformation of oesophageal epithelial cells.[122] The risk of oesophageal carcinoma varies substantially, ranging from ten to 50 times in patients with achalasia compared with the general population.[43,123–129] In a large long-term prospective trial, a hazard ratio of 28 was reported for development of oesophageal squamous-cell carcinoma in patients with achalasia compared with matched control individuals.[129]

Because one of the main symptoms of oesophageal carcinoma, dysphagia, is frequently attributed to exacerbation or recurrence of achalasia, diagnosis of oesophageal carcinoma is often delayed, explaining the poor prognosis in achalasia.[130] This situation raises the question of whether an endoscopic surveillance programme should be initiated for early detection of cancer. However, so far no consensus
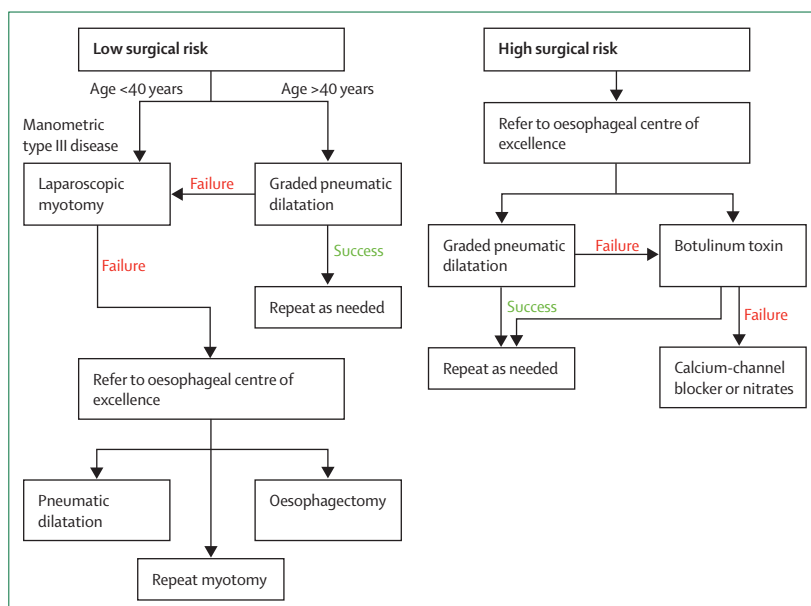

Figure 6: **Proposed therapeutic algorithm for achalasia**
Modified from Richter and Boeckxstaens.[2]

on this topic has been reached for several reasons.[131] First, the death rate from oesophageal cancer diagnosed during a surveillance programme is not different from that of the normal population.[129] Second, endoscopic surveillance is difficult in patients with achalasia because the whole segment is at risk, the mucosa is often covered with food debris and has a cobblestone appearance, and random biopsies might not be representative. Third, the cost-effectiveness of a surveillance programme is dubious because the incidence of cancer is low. However, screening programmes undertaken so far used standard white light endoscopy.[43,123–129] With the introduction of high-resolution endoscopy and chromoendoscopy with Lugol's staining, the sensitivity to detect premalignant lesions has significantly improved.[132] In a recent study, Lugol's staining detected more dysplastic lesions than did white light endoscopy in patients with longstanding achalasia.[133] These lesions were detected in patients diagnosed with achalasia for more than 20 years. Hence, a possible screening strategy could be to start an endoscopic surveillance programme 10 years after initial treatment using Lugol's staining,[133] particularly in high-risk patients (ie, men);[128,134] however, more studies are needed. An additional (but costly) strategy might be to use biomarkers such as p53, which precede the appearance of oesophageal carcinoma in patients with achalasia by several years.[135]

How to predict need for retreatment

Nearly 90% of patients with achalasia can return to near normal swallowing and good quality of life with present treatments.[136] However, few are cured with one treatment, many relapse over time, and intermittent top-up procedures might be needed. How can we predict which patients will need re-treatment? Physiological studies are the best predictors of long-term success of treatment. Eckardt and colleagues[74] reported that all patients with a post-procedure LOS pressure less than 10 mm Hg were in remission after 2 years, 71% were in remission for pressures between 10 and 20 mm Hg, and 23% for pressures over 20 mm Hg. More recently, Hulselmans and colleagues[39] noted that 66% of patients with post-procedure LOS pressure less than 15 mm Hg were in symptomatic remission after 6 years.

The timed barium oesophagram assesses upright oesophageal emptying over 5 min, is readily available, is non-invasive,[50] and is a better predictor of success than is LOS pressure if there is good oesophageal emptying even if LOS pressure was below 10 mm Hg.[75] Vaezi and colleagues[49] reported that patients with complete symptom relief associated with marked improvement in oesophageal emptying were more likely to do well at 3 years than those with symptom relief but poor oesophageal emptying (82% *vs* 10%, respectively). This finding was confirmed in the prospective European Achalasia Trial[79] and was shown in a subsequent analysis to be more predictive of success than post-treatment LOS pressure, with a sensitivity of 88% versus 20%.[75]

More recently, these investigators used the new Endoflip system (MMS, Enschede, Netherlands), which measures the distensibility of the oesophagogastric junction with a balloon catheter passed across the LOS, to measure the cross-sectional area of the sphincter using impedance planimetry.[137,138] In patients with achalasia, oesophagogastric junction distensibility was associated with oesophageal emptying by barium and a low total symptom score and was significantly increased with treatment. Patients with normal oesophagogastric junction distensibility (>2·9 mm²/mm Hg) usually had complete upright oesophageal emptying by 5 min, whereas those with persistent impaired distensibility had a mean barium column height of 5–8 cm at 5 min.[137]

On the basis of these data, we believe that all patients, irrespective of treatment or symptoms, need physiological follow-up of their achalasia. Assessment of symptoms and an upright time barium oesophagram done 1–3 months after treatment seems a practical approach. Those with symptom relief and good oesophageal emptying will do well long term and should be followed up on a regular basis (ie, every 2–3 years). Those with persistent symptoms, poor oesophageal emptying, or both warrant further treatment or close follow-up at 1 year.

Future treatment

Present approaches used to treat achalasia destroy the LOS rather than try to correct the underlying abnormality and to restore function. Assuming that the disappearance of myenteric neurons results from an immune-mediated process, one could theoretically consider immune modulatory drugs. However, at the time of diagnosis the number of neurons has already decreased to a critical level, questioning whether arresting the inflammatory process will restore function. However, a recent case report of a patient with achalasia and eosinophilic oesophagitis showed improved oesophageal motility and disappearance of dysphagia after treatment with 50 mg prednisolone.[139]

An alternative possible treatment option is transplantation of neural stem cells. Recent advances in stem-cell research will hopefully shift treatment towards functional recovery.[140] In particular, the discovery that neural stem cells (or so-called neurospheres) can be isolated and cultured from mucosal biopsies[141] will undoubtedly provide new options for treatment of aganglionic gastrointestinal diseases, including achalasia. Metzger and colleagues[141] generated neurosphere-like bodies from mucosal biopsies capable of proliferating and generating multiple neuronal subtypes. On transplantation, neurosphere-like bodies colonised cultured aganglionic human hindgut to generate ganglia-like structures and enteric neurons and glia. Comparable findings were reported by another group;[142,143] however, after transplantation in vivo into the mouse pylorus, the grafted neurosphere-like bodies failed to adopt a neuronal phenotype.[142] More research

is needed to optimise the technique of stem-cell transplantation before achalasia can really be cured, but there is definitely light at the end of the tunnel.

Contributors
GEB designed the outline of the manuscript. All authors did the literature search, data analysis, provided figures or tables, wrote part of the manuscript, and revised and approved the final manuscript.

Conflicts of interest
We declare that we have no conflicts of interest.

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