Management of achalasia

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Abstract: Several theories on the etiology and pathophysiology of achalasia have been reported but, to date, it is widely accepted that loss of peristalsis and absence of swallow-induced relaxation of the lower esophageal sphincter are the main functional abnormalities. Treatment of achalasia often aims to alleviate the symptoms of achalasia and not to correct the underlying disorder. Medical therapy has poor efficacy, so patients who are good surgical candidates should be offered either laparoscopic myotomy or pneumatic balloon dilatation. Their own preference should be included in the decision-making process, and treatment should meet the local expertise with these procedures. Laparoscopic surgical esophagomyotomy is a safe and effective modality. It can be considered as initial management or as secondary treatment if the patient does not respond to less invasive modalities. Pneumatic dilatation has proven to be a safe, effective, and durable modality of treatment when performed by experienced individuals, and appears to be the most cost-effective alternative. For patients with multiple comorbidities and for elderly patients, who are not good surgical candidates, endoscopic injection of botulinum toxin should be considered a safe and effective procedure. However, its positive effect diminishes over time, and the need for multiple repeated sessions must be taken into consideration. In the management of patients with achalasia, nutritional aspects play an important role. When lifestyle changes are insufficient, it is necessary to proceed to percutaneous gastrostomy under radiological guidance. In the future, intraluminal myotomy or endoscopic mucosectomy will possibly be an option. Further studies are needed to investigate the role of immunosuppressive therapies in those cases in which an autoimmune etiology is suspected.

Keywords: achalasia, esophageal sphincter, botulinum toxin A, dilation

Introduction

Achalasia is a rare motor disorder of the esophagus and lower esophageal sphincter. More specifically, it is a neuromuscular disorder characterized by degenerative changes of the myenteric plexus leading to a selective loss of inhibitory nerve endings. Irreversible disruption of peristaltic contractions and impaired relaxation of the lower esophageal sphincter in response to deglutition are the consequences of this damage.1

Primary idiopathic achalasia is a quite rare disease, with an incidence of approximately 1/100,000/year and a prevalence rate of 10/100,000. Primary achalasia in children is part of the Allgrove’s and Alport’s syndromes, and is more frequent in Down’s syndrome.2

Secondary achalasia shares clinical features with primary achalasia, but there is always an identifiable cause. Worldwide, the most common cause of secondary achalasia is protozoal infection by Trypanosoma cruzi, found in Central and South America.
An association with Class II human leukocyte antigens and some viral infections has been described. An autoimmune pathogenesis in achalasia has been sustained due to the description of antimitenteric neuron antibodies in a subset of patients.

When achalasia is caused by infiltration of the lower esophageal sphincter, by malignancy, or by diseases such as amyloidosis, or as a result of a paraneoplastic syndrome, the term pseudoachalasia is used. Malignancies lead to pseudoachalasia most commonly by direct invasion into the esophagus and lower esophageal sphincter (most commonly gastrointestinal adenocarcinoma, but also oat cell carcinoma, bronchogenic carcinoma, esophageal squamous cell carcinoma, or lymphoma) or by a paraneoplastic phenomenon without cancerous involvement of the lower esophageal sphincter.

An achalasic picture may be mimicked by complications of surgery involving the gastroesophageal junction that may lead to impaired passage of esophageal contents into the stomach, and esophageal dilatation, such as fundoplication, gastric banding, and as a result of injury to the vagus nerve.

From the clinical point of view, achalasia is a progressive disease that presents with symptoms of dysphagia both for liquid and solid foods, chest pain and regurgitation of undigested foods that occurs during meals, shortly thereafter or hours later when the patient changes into the recumbent position. More subtle symptoms include slowing of the speed of eating and stretching or side-to-side movement, as well as walking around after meals to accomplish bolus passage through the nonperistaltic esophagus and across the hypertonic lower esophageal sphincter. Aspiration of food from the esophagus may lead to pneumonia. Loss of weight and malnutrition are uncommon, but they may occur in advanced disease and in elderly patients.

All patients with dysphagia should undergo upper gastrointestinal endoscopy and radiology to rule out anatomic lesions as the first diagnostic step. Diagnostic accuracy is provided only by esophageal manometric studies in over 96% of cases showing a typical pattern both in primary achalasia and pseudoachalasia.

The treatment of achalasia has traditionally relied on a surgical approach. The advent of minimally invasive surgery with a shorter hospital stay, reduced morbidity, and faster return to daily activity, makes this option even more attractive. In contrast, there is evidence that some medical and nonsurgical strategies may be of benefit in many patients with this disorder. This review summarizes the current knowledge and future perspectives for the management of achalasia.

**Pathophysiology**

Although a full description of the complex and still poorly understood mechanisms that underlie achalasia are not the aim of this review, a brief summary of these is useful in order to comprehend the rationale of different treatment options.

The hallmark of achalasia is failure of complete lower esophageal sphincter relaxation. The mechanism of lower esophageal sphincter relaxation is complex, requiring the coordinated interaction of nerves, smooth muscle, interstitial cells of Cajal (ICC), and hormones. Coordinated peristaltic waves that move the food bolus through the distal esophagus depend on excitatory and inhibitory input from local enteric reflexes that originate in the enteric nervous plexus and from extrinsic parasympathetic nerves. The peristaltic reflex involves both cholinergic and peptide excitatory neurotransmission, resulting in contraction of both circular and longitudinal muscle proximal to the bolus, preceded by aboral relaxation ahead of the bolus. While acetylcholine mediates the majority of the neurotransmission between the vagus and intrinsic neurons, it appears that more than one neurotransmitter plays a role between the inhibitory myenteric neuron, ICC, and smooth muscle. A variety of mediators have been proposed, but the main inhibitory factor is nitric oxide. Thus, the nitric oxide-releasing inhibitory neurons are the target in idiopathic achalasia. The triggering event that leads to ganglion cell degeneration in achalasia is still unclear, but loss of nitric oxide-secreting neurons leads to an imbalance between the excitatory and inhibitory neurons of the myenteric plexus, producing irreversible manometric changes in such patients.

Intramuscular ICC have been clearly identified in the lower esophageal sphincter. ICC in the gastrointestinal tract have several different functions, serving as pacemakers, as generators of a smooth muscle hyperpolarizing factor, as mechanic sensors, and as mediators of neurotransmission. Together with the loss of myenteric neurons, a reduction in the number of ICC in the lower esophageal sphincter region has also been reported in idiopathic achalasia. While ICC have an established role in mediating nitrogen and cholinergic neurotransmission in other regions of the gastrointestinal tract, defining the role of ICC in normal lower esophageal sphincter function will require further work.
Treatment options

Treatment of achalasia focuses on relaxation or mechanical disruption of the lower esophageal sphincter. Achalasia is a fairly rare disease, so there are few randomized and controlled clinical trials to define the optimal strategy to treat it. Safety, effectiveness, and durability of current treatment options vary widely.

The progression of achalasia is due primarily to the resistance to the passage of bolus through the poorly relaxing and opening lower esophageal sphincter. If achalasia is left untreated, a dilated esophagus with severe bolus transit impairment will develop, and that condition signals high risk for aspiration pneumonia or perforation. Therefore, the goal in the management of achalasia is an early diagnosis and treatment before reaching this end-stage phase, when surgery becomes mandatory, but usually with a poor outcome. An overview of the current therapeutic options in achalasia is summarized in Table 1.

Pharmacologic therapy

Pharmacologic therapy for the treatment of achalasia would be preferable to the more invasive options for treatment. Unfortunately, such treatment does not eliminate the underlying disease process, but only temporarily leads to lower esophageal sphincter relaxation and may improve symptoms. Nowadays, medical therapy includes nitrates, calcium channel blockers, and nitric oxide donors in an attempt to either facilitate lower esophageal sphincter relaxation and/or enhance esophageal peristalsis.

Calcium channel blockers and nitrates, usually taken 30–60 minutes before meals, have traditionally been the focus of pharmacologic therapy. Calcium channel blockers inhibit cellular uptake of calcium, and because intracellular calcium is necessary for lower esophageal sphincter contraction, relaxation occurs. Calcium channel blockers have been evaluated in the long-term treatment of achalasia, but the use of these drugs often induces tolerance, which severely diminishes the effects over the time. Nifedipine has been shown to induce long-term remission and even normalization of physiology in a minority of patients. Verapamil has been shown to decrease lower esophageal sphincter pressure, but did not demonstrate a relevant symptomatic improvement.

Nitrate therapy acts by counteracting the decrease in the inhibitory neurotransmitter, nitric oxide. This leads to a decrease in lower esophageal sphincter tone, with a subsequent decrease in lower esophageal sphincter pressure. Sublingual isosorbide dinitrate has been shown to decrease the basal lower esophageal sphincter pressure and to improve esophageal emptying. A recent meta-analysis regarding the use of nitrates in the treatment of achalasia have found too low a number of controlled studies, with heterogeneous data, and considerable reported side effects, so was unable to recommend clinical use of these drugs for the disease.

Endoscopic therapies

Endoscopic therapies include botulinum toxin injection into the muscular layer of LES and pneumatic dilation of the hypertonic LES. Botulinum toxin injection improves passive esophageal emptying and aims at fracturing the fibers of the muscularis propria. Pneumatic dilation can induce long-term remission and even normalization of physiology in a minority of patients. Esophageal perforation or rupture, bleeding, and local pain are possible complications.

Surgery

Surgical intervention in the form of laparoscopic Heller myotomy plus antireflux fundoplication is a widely performed procedure. The myotomy involves deep disruption of muscular hypertonic fibers in the LES. Although the most "pathophysiologic" solution, it is costly; possible postoperative complications include gastroesophageal reflux and Barrett's esophagus.

Table 1 Current therapeutic options for achalasia

<table>
<thead>
<tr>
<th>Therapeutic modality</th>
<th>Mode of action</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacologic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroprusside (isosorbide)</td>
<td>Inhibition of muscle contraction, induction of relaxation, promotes esophageal emptying</td>
<td>Hypotension, headache, drowsiness</td>
</tr>
<tr>
<td>Calcium channel blockers (nifedipine, verapamil)</td>
<td>Induction of NO release, reduction of LES pressure</td>
<td>Hypertension, angina</td>
</tr>
<tr>
<td>S phosphodiesterase inhibitors (sildenafil)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopic therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botulinum toxin (injection into the muscular layer of LES)</td>
<td>Potent inhibition of the release of acetylcholine, improves passive esophageal emptying</td>
<td>Feasible and safe on an outpatient basis;</td>
</tr>
<tr>
<td>Pneumatic dilation of the hypertonic LES</td>
<td>Aims at fracturing the fibers of the muscularis propria</td>
<td>Heller myotomy could be more difficult in patients that underwent repeated injections</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopic Heller myotomy plus antireflux fundoplication</td>
<td>Deep disruption of muscular hypertonic fibers in the LES</td>
<td>Although the most “pathophysiologic” solution, is costly; possible postoperative complications</td>
</tr>
<tr>
<td>Esophagogastrectomy with gastric or colonic interposition</td>
<td>Total modification of the LES anatomy; to be left for end-stage illness</td>
<td>Gastroesophageal chronic reflux and Barrett’s esophagus</td>
</tr>
</tbody>
</table>

Abbreviations: LES, lower esophageal sphincter; NO, nitric oxide.
blockers are still more widely used. Table 2 summarizes the data and the results of chronic prospective and controlled studies involving the use of calcium channel blockers and nitrates in achalasia.

Sildenafil, a 5-phosphodiesterase inhibitor that reduces the breakdown of cyclic GMP, the second messenger mediating nitric oxide-induced relaxation, has been proposed as an alternative pharmacologic agent for the treatment of achalasia. Experimental data demonstrate its ability to decrease lower esophageal sphincter tone and residual pressure. Further studies are needed to determine whether this might be of clinical utility in achalasia.

Although a clinical guideline for the management of achalasia is still not available, we can assume that pharmacologic therapies presently have very limited value in its treatment. However, the use of sublingual nifedipine before meals seems to remain solely indicated for patients not willing or unable to undergo any other procedure and/or waiting for a more definitive therapy, or as supportive treatment for refractory chest pain.

### Endoscopic therapies

To date, the primary modality of endoscopic therapy for achalasia is the injection of botulinum toxin A into the lower esophageal sphincter. Botulinum toxin A is a potent inhibitor of the release of acetylcholine, which has an excitatory influence on lower esophageal sphincter tone. Injection of botulinum toxin A into the lower esophageal sphincter improves “passive” esophageal emptying by counterbalancing the selective loss of inhibitory neurons in the myenteric plexus, decreasing lower esophageal sphincter pressure, and increasing lower esophageal sphincter opening when compared with injection of placebo.27,28

The mean duration of effect of a single injection of botulinum toxin A is 10–12 months, with a wide variability ranging from three months to three years. The reason for such variability is unknown, but is probably related to another drawback of the toxin, ie, the development of an autoimmune response with the production of antibodies that may, in turn, decrease its efficacy in some patients.

Botulinum toxin A 80–100 U is injected through a 5 mm needle into the lower esophageal sphincter, with aliquots of 20–25 U of the toxin injected into the four quadrants of the lower esophageal sphincter. The procedure is no more demanding than a routine endoscopy, and apart from occasional complaints of transient chest pain, patients tolerate it very well. They can go home after they recover from sedation and are allowed to eat soft foods later in the day. Symptomatic improvement occurs gradually and usually peaks 1–3 days later, although this may be delayed even further in the occasional patient.

Following a single treatment with botulinum toxin A, relief of symptoms has been reported in almost 80% of patients. After six months, 50% of patients may remain in remission, while others will need repeated injections, or other treatment options, such as pneumatic dilation or surgical myotomy.

Annese28 reported a success rate of 68% at 24 months after repeated administration of botulinum toxin A injection, while Pasricha29 found a 30% efficacy rate after a mean follow-up of two years. Injection of botulinum toxin A seems to be simple and safe, without carrying any risk of perforation.30 Post-treatment evaluations have revealed that neither pretreatment lower esophageal sphincter pressure, amplitude of esophageal contractions, nor duration of illness could be used to predict the outcome of botulinum toxin A injection. Instead, young age and male gender were found to affect the outcome adversely.

Surgeons have reported that Heller myotomy could be more difficult in patients who undergo repeated botulinum toxin A injection, due to increased adhesion of the muscular layer, but, so far, this therapeutic option has to be chosen as a first step in all patients who are eligible for it.31 In contrast, botulinum toxin A is widely demonstrated to be the most

### Table 2

Clinical studies with calcium channel blockers and nitrates in achalasia

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Patients (n)</th>
<th>Efficacy (%)</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelfonc 1981</td>
<td>Isosorbide</td>
<td>24</td>
<td>79</td>
<td>2–19</td>
</tr>
<tr>
<td>Silverstein 1982</td>
<td>Diltiazem</td>
<td>8</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Gelfonc 1982</td>
<td>Nifedipine</td>
<td>15</td>
<td>53</td>
<td>8–18</td>
</tr>
<tr>
<td>Bortolotti et al</td>
<td>Nifedipine</td>
<td>20</td>
<td>90</td>
<td>6–18</td>
</tr>
<tr>
<td>Traube 1992</td>
<td>Nifedipine</td>
<td>14</td>
<td>65–80</td>
<td>6</td>
</tr>
<tr>
<td>Coccia 1992</td>
<td>Nifedipine</td>
<td>14</td>
<td>77</td>
<td>21</td>
</tr>
<tr>
<td>Triadafilopoulos</td>
<td>Nifedipine</td>
<td>14</td>
<td>NA</td>
<td>10</td>
</tr>
<tr>
<td>Triadafilopoulos</td>
<td>Verapamil</td>
<td>14</td>
<td>NA</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.
effective treatment option in elderly patients or in patients with comorbid illnesses, in whom dilatation or surgery is high-risk. Symptom relief was found to last up to 1–2 years with a single injection in the elderly.

Historically, pneumatic dilation was the first attempt at therapy in esophageal achalasia, and was described in 1674 by Sir Thomas Willis. Pneumatic dilation of the lower esophageal sphincter in patients with achalasia aims at fracturing the fibers of the muscularis propria. Bougienage or a “standard” balloon for dilation are typically ineffective, but pneumatic dilation with a rigid and high-sized balloon across the lower esophageal sphincter has been shown to be effective and quite inexpensive. Forceful dilatation of the lower esophageal sphincter is considered to date the most effective nonsurgical treatment for achalasia, although details of the procedure vary in different institutions. While there is no clear consensus on the technical details of balloon dilatation, most leading operators used their own pneumatic dilatation technique passed along from experienced to junior physicians. Inpatient versus ambulatory treatment, sedated versus nonsedated dilatation, the sedative used, the dilator system, initial balloon size, speed, pressure, duration, number of dilations per endoscopic session, and timing of redilations differ from center to center.

Typically, pneumatic dilation is performed over a guide wire under fluoroscopic guidance. This allows for assessment of the progress of dilatation as the narrowed “waist” of the lower esophageal sphincter disappears. However, in addition to radiation exposure, this requires bulky and expensive fluoroscopy equipment, which may be in high demand or not available for general use. Performing pneumatic dilatation under direct endoscopic visualization is a good alternative to fluoroscopic guidance. After placement of the dilator over the guide wire, the endoscope is reintroduced into the esophagus. The balloon placement and dilation effects are observed proximal to the balloon. This method has been performed for more than 20 years, and the American Society of Gastrointestinal Endoscopy has suggested that either visualization method is acceptable for safe dilation in achalasia. Major complications are rare after pneumatic dilation. The most serious complication is esophageal perforation, which occurs at a mean rate of about 2.5%. Gastroesophageal reflux is the most frequent chronic complication after lower esophageal sphincter dilation for achalasia. With 24-hour pH monitoring and esophageal manometry, it is possible to define the pathophysiologic subset of the reflux, because it is nearly always associated with a hypotensive lower esophageal sphincter and ineffective esophageal body motility.

Some investigators debate the role of botulinum toxin A injection versus pneumatic dilation. A recent Cochrane review of six randomized controlled trials including 178 patients evaluated symptom recurrence after esophageal dilation versus endoscopic botulinum toxin A injection at one, six, and 12 months after treatment. Thirty percent of patients undergoing dilation experienced symptom recurrence and treatment failure at 12 months versus 74% of patients who received botulinum toxin A. Furthermore, a systematic review and meta-analysis of 105 papers that reported on 761 patients with achalasia who underwent endoscopic treatment with esophageal dilation or botulinum toxin A showed that symptom relief was better for dilation, and the necessity for further treatment was significantly reduced.

Surgery

Minimally invasive surgical techniques have dramatically modified the management algorithm of the treatment of achalasia. The advantage of a less invasive, safe, and effective surgical option prompts gastroenterologists to choose patients earlier for surgery, because this obviates the need for dilation.

Currently, the standard surgical management for achalasia is the laparoscopic Heller myotomy, first reported in 1991. This technique is associated with the greater decrease in dysphagia, a shorter hospital stay, lower risk of postoperative gastroesophageal reflux, and low complication rates. An antireflux procedure can further reduce postoperative heartburn rates by 80%, as well as the risk of esophagitis and peptic stricture. A Dor or Toupet fundoplication reduces reflux as well as a Nissen procedure, but the partial wraps trend toward less dysphagia. The dysphagia rate attributed to fundoplication ranges from 0% to 8%. Failure of improvement with dilatation suggests incomplete myotomy and a requirement for repeat manometry. Optimal length of the cardiomyotomy is at least 2 cm. Although a Dor fundoplication is more commonly reported, the choice of Toupet versus Dor depends on surgeon preference. There are very few randomized prospective trials examining esophagomyotomy versus pneumatic dilation. One study showed equivalent effectiveness at relieving symptoms initially, but at follow-up it showed those patients who had esophagomyotomy had fewer recurrent symptoms than those who had pneumatic dilatation. Very recent preliminary data from a large and powerful multicenter randomized clinical trial comparing the treatment success of these two different therapies suggest that, after two years of follow-up, pneumatic dilatation and laparoscopic myotomy have a comparable success rate.
of 87%–92%. Some studies suggest that pneumatic dilation may achieve long-term relief of symptoms in patients older than 50 years.\(^5\)\(^1\)

Despite symptom improvement by either pneumatic dilation or surgical myotomy in achalasia patients, 10%–15% of those so treated will present with progressive deterioration in their esophageal function, and up to 5% may eventually require an esophagectomy. The optimal reconstruction for the resected esophagus should be gastric interposition, colon interposition, and jejunal interposition, all of which have their respective advantages and disadvantages.\(^5\)\(^2\),\(^5\)\(^3\) It is questionable if progression to esophageal cancer following Heller myotomy (adenocarcinoma in Barrett’s esophagus or squamous cell carcinoma) is a failure of surgery or a failure of follow-up. Development of adenocarcinoma after myotomy in the sequelae of Barrett’s esophagus might be due to a too long myotomy, and only few case reports on this association are available.\(^5\)\(^4\)

### Nutritional approach

The management of the patient with achalasia and nutritional problems is very similar to that of patients with dysphagia due to neurologic disease or esophagogastric cancer.\(^5\)\(^5\),\(^5\)\(^6\) Oral feeding has relevant psychosocial significance to patients and their families, and should be continued whenever possible. In some patients, oral intake is often not adequate even in the absence of significant swallowing difficulties. In mild to moderate achalasia, nutrition is generally mildly affected and, if the family encourages the patient to follow dietary modifications, loss of weight and malnutrition rarely occurs.

Dysphagia diets should be highly individualized, including modification of food texture or fluid viscosity. Food may be chopped, minced, or puréed, and fluids may be thickened.\(^\)\(^5\)\(^7\)

If a patient is unable to eat or drink or to consume sufficient quantities of food, or the risk of pulmonary aspiration is high, tube feeding should be provided. If there is a possibility for surgical myotomy, enteral nutrition via a nasal feeding tube will be adequate as a provisional measure, considering that a malnourished patient is always at major risk for postoperative complications. In very rare and selected cases of end-stage achalasia, in which there is any further possibility of surgery or pneumatic dilation, the insertion of the feeding tube through a percutaneous radiologic gastrostomy rather than a surgical gastrostomy would be the treatment of choice. Percutaneous gastric tube feeding is effective and usually acceptable to patients and their carers. Long-term complications include tube obstruction and wound infection. In some patients who are fed via a gastric tube, pulmonary aspiration may occur and routine intrajejunal feeding has been suggested for these cases.\(^5\)\(^8\)

### Possible future therapies

The utility of self-expanding 30 mm endoscopic metallic stents for achalasia has been prospectively evaluated in 75 patients at a single center over a 13-year period. The clinical success rate after 10 years of follow-up after the stent was removed was high (83%). There were no perforations or mortality associated with the treatment, but stent migration occurred in 5% of patients, reflux in 20%, and chest pain in 38.7%.\(^5\)\(^9\)

Pasricha reported a method of submucosal endoscopic myotomy with no skin incision in an experimental model.\(^5\)\(^9\)

More recently, Inoue described a clinical application of modified Pasricha technique as per oral endoscopic myotomy (POEM) to provide a less invasive permanent treatment for esophageal achalasia.\(^6\)\(^0\)

Thirty-five achalasia patients who had lasting symptoms of dysphagia received POEM.\(^6\)\(^1\) Barium swallows before and after the procedure demonstrated total release of thickened lower esophageal sphincter. Mean operating time was about 120 minutes and the mean hospital stay after the procedure was 4.9 days. No severe complication was reported and dysphagia symptoms disappeared after the procedure. Mean resting pressure of the sphincter fell. Subjective symptom score was significantly improved in all cases. This method is achieved with the already available techniques and devices for routine endoscopic myotomy. This procedure allows a direct approach to the thickened inner muscular layer with no skin incision and effectively releases lower esophageal sphincter pressure. Myotomy length can be flexibly determined according to the patients’ symptoms, such as dysphagia and chest pain. This seems to be a very promising technique possibly leading to a new frontier for endotherapy of achalasia, but further studies of the long-term efficacy and a comparison of POEM with other interventional therapies are awaited.\(^6\)\(^2\)

In view of the fact that the enteric neurons innervating the esophagus and the lower esophageal sphincter could disappear due to an autoimmune mechanism, immunosuppressive therapy could prevent disease progression.\(^6\)\(^3\) However, at the time of diagnosis, the number of neurons has already decreased, leading to significant dysfunction and symptoms. Although this approach may theoretically prevent further disappearance of neurons, it is possible that comes too late and will fail to restore function.
Recent experimental studies in mice suggest that transplantation of neuronal stem cells might be a future therapeutic option. Indeed, neuronal stem cells injected in the pylorus survived and even expressed nitric oxide synthase. The advantage of such a technique would be that not only would sphincter function be restored, but perhaps even peristalsis too. That is a very suggestive hypothesis, and clearly a lot of research remains to be done further exploring this approach.

**Decision-making and cost-effectiveness**

The appropriate treatment for any given patient with achalasia depends on their willingness to undergo invasive procedures and on their physical ability to endure them. A decision analysis model has been developed for the treatment of achalasia. Four therapeutic options were evaluated, ie, laparoscopic Heller myotomy and partial fundoplication, pneumatic dilation, botulinum toxin injection, and thoracoscopic Heller myotomy. Based on complications, need for repeated procedures, and overall treatment cost, it has been found that laparoscopic Heller myotomy with fundoplication was the preferred treatment strategy. The authors recommended that those patients who meet diagnostic criteria for achalasia (manometric, endoscopic, radiographic) in a referral center and who are good surgical candidates should be referred to an experienced surgeon for minimally invasive modified Heller myotomy. Patients who are not good surgical candidates and cannot accept the risk of pneumatic dilation can be treated with single-shot or repeated botulinum toxin A injection or can be treated with pharmacological agents.

Several cost analyses have been performed to verify which modality of treatment is the most cost-effective. Multiple studies evaluating the cost of the initial 5–10 years of therapy have demonstrated that pneumatic dilatation is the most cost-effective modality in otherwise healthy populations. In patients with other comorbidities that decrease life expectancy, botulinum toxin A is more cost-effective. Although surgery seems to be the most definitive and effective treatment for achalasia, it appears to be costly over the initial years of therapy.

**Summary**

Although the ultimate goal of the treatment of esophageal achalasia should be the restoration of esophageal peristalsis and lower esophageal sphincter relaxation, at present there is not a known therapeutic option addressing this goal, and both gastroenterologists and surgeons continue to destroy the lower esophageal sphincter. Whereas medical therapy has poor, if any, results, Heller myotomy and pneumatic dilatation are successful in 70%–90% of patients in the first year, but the success rate slowly declines with time. Botulinum toxin injection in the lower esophageal sphincter is safe and effective, but it has to be reserved for elderly patients with comorbid illnesses. Pneumatic dilation or Heller myotomy seems to be the best solution, each modality having technical problems and possible complications. Which of these treatments might be the therapy of choice for achalasia in particular subgroups of patients remains to be investigated. Clearly, more research is required to develop therapies to restore the functional anatomy of the lower esophageal sphincter.

**Disclosure**

The authors report no conflicts of interest in this work.

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