ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Diffuse Esophageal Spasm in the Era of High-Resolution Manometry

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G&H What is diffuse esophageal spasm?

SA Historically, the term "diffuse esophageal spasm" (DES) has been used to describe a motility disorder of the smooth muscle of the esophagus that is associated with chest pain and/or dysphagia. A recent study by Sperandio and colleagues examined the location of motility abnormalities in the esophagus and found that the majority are confined to the smooth muscle of the distal esophagus; thus, the researchers proposed that the condition instead be called "distal esophageal spasm." Accordingly, DES, "esophageal spasm," and "distal esophageal spasm" may be used interchangeably.

G&H Could you discuss the evolution of the understanding of this disorder?

SA DES was first reported in 1889 by Osgood in 6 patients who presented with chest pain and dysphagia. In the 1950s, a combination of clinical criteria (chest pain/dysphagia) and radiologic features (eg, tertiary contractions or segmentation seen on a barium swallow) were used to define the condition. However, radiographic studies have poor diagnostic sensitivity, as they show variable day-to-day appearance and have insufficient correlation with symptoms. Radiographic protocols also lack standardization in terms of volume and the number of swallows used during the study.

Creamer and colleagues (in 1958) and Roth and Fleshler (in 1964) made the first manometric descriptions of DES, in which esophageal motility was characterized as frequent, simultaneous, and excessively long contractions in the distal esophagus with intermittent primary peristalsis. In 1974, a seminal study by Richter and Castell identified all case series of patients with DES at the time. After analyzing 12 studies and examining multiple manometric features, the authors concluded that the most consistent diagnostic criterion was the presence of simultaneous contractions in more than 10% of wet swallows alternating with normal peristalsis. The authors supported this observation further by establishing that no persons in a large group of healthy controls (n=95) had more than 10% of simultaneous contractions. Additionally, ineffective motility was recognized as a motility disorder in which the amplitude of contractions in the distal esophagus is less than 30 mmHg and in which contractions may occur simultaneously, thus resembling DES and leading to the need to distinguish esophageal spasm from ineffective motility. Therefore, the amplitude of the simultaneous contractions in DES must be at least 30 mmHg.

G&H How has high-resolution esophageal pressure topography affected the diagnostic criteria for DES?

SA In 2000, with the introduction of high-resolution esophageal pressure topography (HREPT), it was proposed that the definition of DES be modified. Initially, the Chicago classification recommended that the defining criterion for DES using HREPT be based on rapid contractions (the equivalent of simultaneous contractions during conventional line pressure motility), which were defined by using the metric of contractile front velocity (CFV; >8 mm/s). However, CFV has been found to be

susceptible to regional variability in contractile velocity within the swallow and, thus, is a nonspecific finding of unknown significance.

The distal latency (DL) parameter appears to be a more reliable measure of premature contractions. DL is likely a reflection of inhibitory myenteric neuron activity involved in the timing of contraction in the distal esophagus. DL is shorter in patients with simultaneous contractions than in those with normal peristaltic propagation. This parameter is measured from the onset of the pharyngeal swallow to the onset of the contraction in the distal esophagus. During HREPT, DL is defined as the interval between upper esophageal sphincter relaxation and the contraction deceleration point (CDP), with the latter parameter being defined as the inflection point at which propagation velocity slows, demarcating the tubular esophagus from the esophageal ampulla. A DL of less than 0.4 seconds in 20% of wet swallows coupled with a normal integrated relaxation pressure at the lower esophageal sphincter is considered diagnostic of DES.

G&H What is the suspected pathogenesis of DES?

SA The cause of DES remains unknown. There is a lack of information regarding histopathology of the neuromuscular lesion because patients with DES do not die from the disorder and, thus, are rarely autopsied. Studies using high-frequency endoscopic ultrasound have suggested that there is hypertrophy of the esophageal muscle layer.

Nitric oxide (NO) is involved in the regulation of esophageal peristalsis. Functional studies in animal and human models have found that inhibition of NO induces simultaneous contractions in the distal esophagus, the manometric hallmark of DES, whereas replacement of NO restores normal peristalsis. These studies underscore the role of NO in DES and suggest that impaired neural inhibition is a likely cause of DES. They also explain why nitrates may improve symptoms (by restoring NO) in some patients.

G&H Does gastroesophageal reflux disease play a role in DES?

SA The role of gastroesophageal reflux disease (GERD) in DES has been suggested by several observations. Studies by Siegel and Hendrix in 1963 demonstrated esophageal motility abnormalities induced by acid perfusion in patients with heartburn. Subsequent studies noted that esophageal acid infusion may produce both chest pain and abnormal motility (including simultaneous contractions) in patients with esophageal symptoms but rarely in controls. With the use of high-frequency ultrasound combined with pH monitoring, sustained esophageal contractions have been correlated with GERD. In a recent study of 108 consecutive patients with DES at our center, at least 38% had coexisting GERD. Uncontrolled observations also suggest that subgroups of patients with DES may respond to proton pump inhibitor (PPI) therapy. Clearly, more data are needed to better understand the role of GERD in DES.

G&H How is DES diagnosed?

SA DES should be suspected in patients presenting with unexplained noncardiac chest pain and/or dysphagia. In a recent study of patients with DES, my colleagues and I found that 51% reported having heartburn and 30% experienced weight loss. A barium swallow may show nonspecific tertiary contractions and, occasionally, a more convincing finding such as a cork-screw or rosary-bead appearance (ie, severe luminal obliteration of the barium column). However, as discussed above, barium radiography has a low diagnostic sensitivity.

The current gold standard for the diagnosis of DES is conventional esophageal motility testing. However, the diagnostic sensitivity of esophageal motility is also unknown. This is due to the intermittent nature of DES and the lack of correlation between symptoms and motility. Despite these limitations, the proposed manometric criteria involve the presence of simultaneous contractions in the distal (smooth muscle) esophagus in more than 10% of wet swallows coupled with an amplitude contraction of at least 30 mmHg alternating with normal peristalsis.

Also as discussed, on HREPT, a DL of less than 4.5 seconds in at least 20% of wet swallows associated with normal esophagogastric junction (EGJ) relaxation (≥15 mmHg) has been proposed as the diagnostic criterion for DES. However, as noted by Pandolfino and colleagues, this finding is very rare, occurring in only 24 of 1070 patients at a tertiary center specializing in esophageal motility disorders. Therefore, confirmatory studies from other centers are needed. In addition, treatment outcomes using HREPT (DL) as the diagnostic criteria for DES are also required to support the use of this parameter as a diagnostic marker.

G&H Which other esophageal disorders should be excluded when establishing a diagnosis of DES?

SA Esophageal symptoms of chest pain and/or dysphagia are nonspecific and can occur in other esophageal disorders, such as achalasia, nutcracker esophagus, ineffective motility, hypertensive lower esophageal sphincter, and jackhammer esophagus. GERD should also be carefully excluded because it may contribute to DES or it may just coexist with DES.

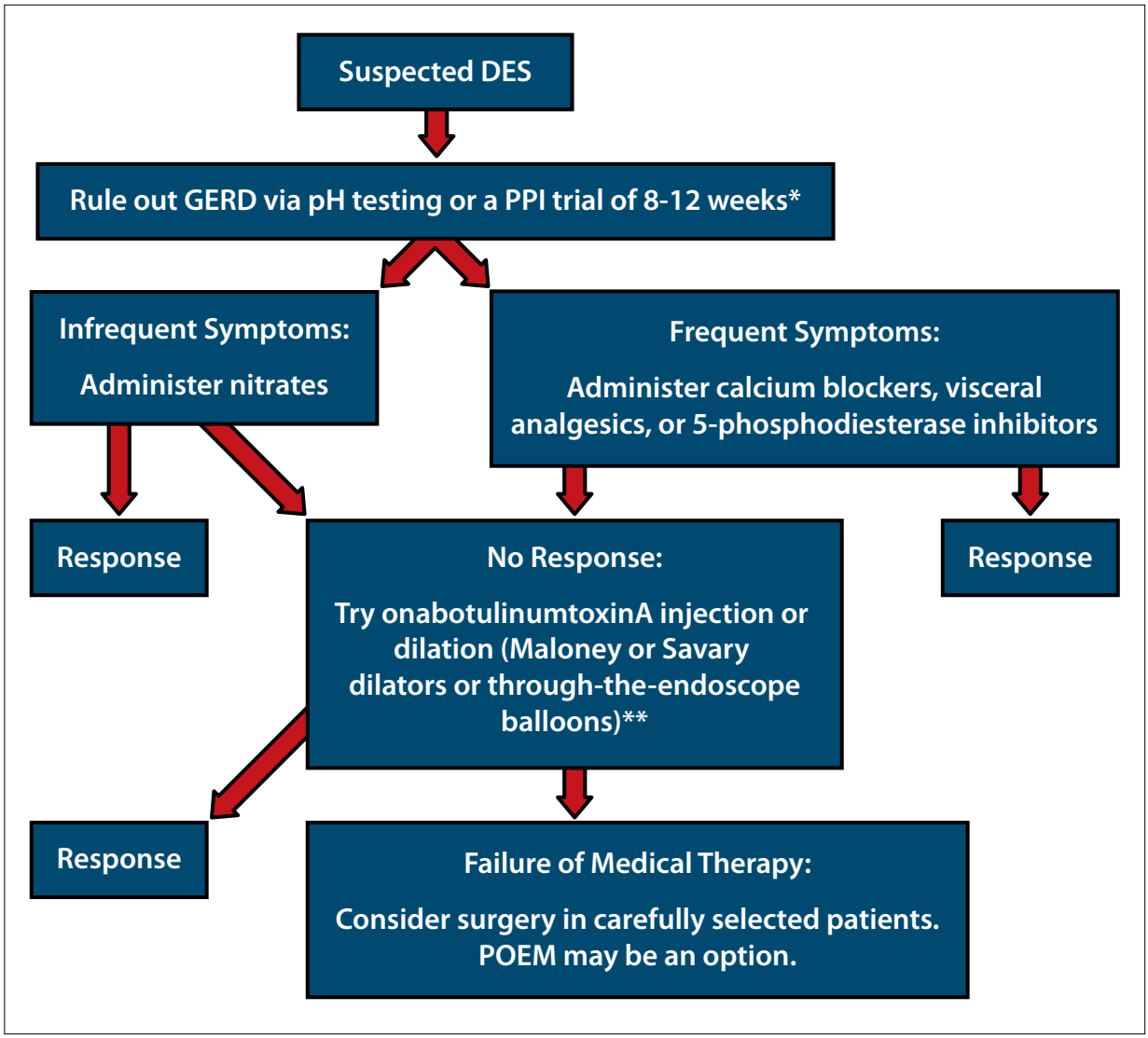

Figure. A treatment algorithm for DES.

*This approach has not been studied in a formal trial. For patients responding to PPIs, offer maintenance therapy. **Dilation with Maloney or Savary dilators or through-the-endoscope balloons has not been studied critically.

DES, diffuse esophageal spam; GERD, gastroesophageal reflux disease; POEM, peroral endoscopic esophageal myotomy; PPI, proton pump inhibitor.

HREPT should be interpreted carefully. Premature contractions (defined by reduced DL) and normal EGJ relaxation characterize DES, whereas reduced DL and impaired EGJ relaxation are the defining criteria for spastic (type III) achalasia on HREPT.

G&H How is DES usually treated?

SA Treatment of DES is imperfect and difficult due to the incomplete understanding of the pathophysiology and cause of this condition. Most published therapeutic trials are small case series or open-label, uncontrolled studies. In addition, clinicians frequently use data from therapeutic trials of patients with noncardiac chest pain or nonobstructive dysphagia due to the lack of studies in DES. Several agents have been used to treat DES with variable degrees of success. The Figure shows a suggested treatment algorithm for DES.

An important initial step of DES treatment is to determine whether a patient has coexisting GERD. An ambulatory pH study or an empirical PPI trial for 8 to 12 weeks is a reasonable starting point. Although there are no published controlled trials regarding this approach, patients with coexisting GERD may benefit from acid suppression instead of muscle relaxants, which may worsen their GERD.

For patients who are not responding to PPIs or who do not have GERD, on-demand nitrates may be pre-

scribed to treat infrequent or intermittent symptoms of chest pain or dysphagia. However, there have not been any controlled studies documenting long-term benefits of nitrates. Peppermint oil (5 drops in 10 mL of water) improved chest pain in a small uncontrolled study.

Calcium blockers such as nifedipine and diltiazem may be used as long-acting agents in patients with more frequent or sustained symptoms. Visceral analgesics such as low-dose tricyclic agents (nortriptyline and trazodone) may also be useful, particularly in patients with chest pain, but there is a lack of clinical controlled trials on this issue. Selective serotonin receptor inhibitors may also be a beneficial long-term therapy, as shown in a small trial of 9 patients.

There is good rationale for using 5-phosphodiesterase inhibitors (sildenafil, vardenafil, and tadalafil) because they increase the bioavailability of NO. In addition, small studies have suggested that sildenafil does not induce GERD. In a study by Fox and colleagues, 2 patients with DES improved after receiving open-label sildenafil (25-50 mg). Large placebo-controlled trials are needed to further evaluate these agents.

For patients who are not responding to pharmacologic therapy or those who are intolerant to medications, onabotulinumtoxinA (Botox, Allergan) therapy could be considered as a second-line treatment. Injection of this medication into the distal esophagus has been effective at relieving symptoms in approximately 72% of patients with various esophageal motility disorders in open-label studies. In the only double-blind, randomized, placebo-controlled study conducted to date, which included 22 patients with a combination of DES and nutcracker esophagus, onabotulinumtoxinA had beneficial effects on dysphagia and weight loss.

G&H What is the role of esophageal dilation in DES?

SA Although it makes sense to consider dilation of the esophagus, particularly in patients with dysphagia, this approach has not been subjected to rigorous trials. The use of bougie dilators or through-the-endoscope balloons has not been critically studied in DES.

Pneumatic balloon dilation for treatment of DES has only been examined in 2 small studies. In a study conducted by radiologists, 14 of 20 patients (70%) improved, and there was 1 esophageal perforation. In the other study, 8 of 9 patients experienced marked improvement in dysphagia and regurgitation, with an average follow-up of 37.4 months. Although physicians may also consider the use of bougie dilation for some patients with dysphagia, there is a lack of data regarding the outcomes of this approach.

G&H How effective is esophageal surgery for treatment of DES?

SA Heller myotomy, which is typically used to treat achalasia, has also been used to treat DES. The available data suggest that this surgery provides an overall beneficial effect, but outcomes are variable. In addition, there is a lack of randomized clinical trials comparing the effects of medical and surgical therapies. The majority of series come from tertiary centers that are highly skilled in the surgical treatment of esophageal diseases. Most patients from surgical series are selected very carefully and usually represent refractory cases to medical therapy. Surgical repair rarely induces restoration of normal peristalsis or complete resolution of radiographic appearance. These data suggest that restoration of motility and relief of symptoms may not be related, and incidental dissection or division of intramural nerve fibers may account for symptom relief. Controlled trials, however, may be difficult to conduct, given the rarity of the disorder.

Peroral endoscopic esophageal myotomy (POEM) is a new technique for the treatment of achalasia. Two case reports (each consisting of 1 patient) suggest that beneficial results may also be obtained in DES. However, there is concern that significant GERD may ensue following POEM. Unlike laparoscopic myotomy, a partial fundoplication cannot be added during POEM to protect against GERD.

Dr Achem has no relevant conflicts of interest to disclose.

Suggested Reading

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