

HEARTBURN & DYSPHAGIA: THE ESOPHAGEAL MOTILITY DISORDERS

Glen E. Hastings, M.D.
May 22, 2005

- I IMPORTANCE¹:** After coronary artery disease, the esophageal motility disorders are the 2nd most common stress-related cause of chest pain. 30% of the 600,000 cardiac catheterizations performed annually show normal coronary arteries. 65% of those have esophageal motility abnormalities. There are 90,000 such patients in the US who spend an estimated \$315 million annually to treat chest pain.
- II SYMPTOMATOLOGY²:** The symptoms caused by the esophageal motility disorders are easily confused with those of coronary artery disease, so the first order of business is to exclude CAD by cardiovascular testing (See the Outline on Stress Testing), especially in patients presenting with chest pain.
- The **combination** of 3 complaints: **chest discomfort, regurgitation** and **dysphagia** occurs at least occasionally in 68% of patients with esophageal dysfunction but in only 10% of cardiac patients.
- The constellation of symptoms presented by any individual patient depends on the cause. Table 1 lists the various esophageal motility disorders along with the symptoms commonly caused by each.
- When the presenting symptom is caused by an **anatomic obstruction**, such as an esophageal web, achalasia or cancer of the esophagus, the patient's subjective perception of the location of the obstruction is quite accurate (predictive value 89%).
- III DEFINITIONS:** It is important that the patient's specific symptoms, signs & diagnoses be described with clarity & precision. The Glossary shown on the next page contains some of the terms commonly used in describing problems of esophageal dysmotility.

Table 1: Differential Symptoms of Esophageal Motility Disorders^{1,2,3,4,5}

Symptom	GERD	Achalasia	Diffuse Esophageal Spasm. Nutcracker & Corkscrew Esophagus	Globus Hysterics	Scleroderma Esophagus	Mucosal Inflammation	Mechanical Obstruction
Heartburn	++++		++		++++		
Regurgitation	+++	+++	+		+++		++
Water Brash	++				+++		
Globus	+	+	++	++++			+
Hoarseness	+			+			+
Noncardiac Chest Pain	++	+	++++	+			
Dysphagia	+	++++	++	++	++	++	++++
Odynophagia		+	+	+	+	+++	+
Halitosis		+++				++	
Sitophobia		++	+			+++	++
Bradycardia/Syncope			+				

IV VARIETIES OF ESOPHAGEAL DYSMOTILITY:

- Gastroesophageal Reflux Disease (GERD)
- Achalasia
- Diffuse Esophageal Spasm (DES)
- Nutcracker Esophagus
- Scleroderma Esophagitis
- Mucosal Infections & Inflammation
- Mechanical Obstruction

V DIAGNOSTIC TESTS:

- Endoscopy is the "gold standard" for identifying mucosal abnormalities.
- Double contrast esophagoscopy is the "gold standard" for demonstrating esophageal diverticula, strictures and anatomic abnormalities.
- Pressure manometry is the "gold standard" for demonstrating motility abnormalities.
- 24 hour esophageal pH monitor is the "gold standard" for GERD (sensitivity: 86%, specificity: 0.97).
- Provocative tests include:
 - Bernstein Test (0.79 sensitivity, 0.82 specificity for esophageal reflux).
 - Edrophonium challenge for reproducing noncardiac chest pain.

GLOSSARY

ACHALASIA	An esophageal motor abnormality characterized by aperistaltic esophageal contractions & a hypertensive, incompletely relaxing esophageal sphincter, frequently presenting with dysphagia or chest pain.
APERISTALSIS	Failure of the synchronized forward propelling gut contractions either resulting from the absence of contractions or the presence of simultaneous non-peristaltic contractions
DEGLUTITION	Swallowing
DIFFUSE ESOPHAGEAL SPASM (DES)	A manometric diagnosis based upon the synchronous occurrence of nonperistaltic esophageal contractions that are synchronous with chest pain. “Corkscrew Esophagus” is a variant of DES.
DYSPEPSIA	Epigastric discomfort, fullness, bloating, or burning quality, sometimes associated with belching, anorexia, nausea, vomiting or food intolerance without bowel habit change
DYSPHAGIA	Discomfort with swallowing. Dysphagia at the upper esophageal sphincter presents with choking or regurgitation of swallowed liquids through the nose. Lower obstruction produces the sensation of “sticking” in passage, which is the hallmark of mechanical obstruction or motility dysfunction
GASTROESOPHAGEAL REFLUX DISEASE (GERD)	Does not necessarily imply histological changes in the esophagus. Minor degrees of GERD may consist only of the symptoms of heartburn occurring synchronously with acid reflux into the esophagus causing a transient pH drop below 4.0.
GLOBUS	The subjective sensation of a “lump in the throat that won’t go down”.
NUTCRACKER ESOPHAGUS	A manometric diagnosis based upon the synchronous occurrence of chest pain & peristaltic esophageal contractions of supranormal intensity (>150 mm Hg) but of otherwise normal configuration, which may frequently be reproduced by edrophonium challenge
ODONOPHAGIA	Pain on swallowing. A hallmark of mucosal inflammation or esophageal dysmotility
REFLUX ESOPHAGITIS	Inflammatory changes in the esophageal mucosa caused by prolonged exposure to acid or bile
SITOPHOBIA	Fear of eating
WATER BRASH	The belching up of copious liquid saliva & acidic gastric secretions often while lying supine.

VI GASTROESOPHAGEAL REFLUX DISEASE (GERD)^{2,3}:

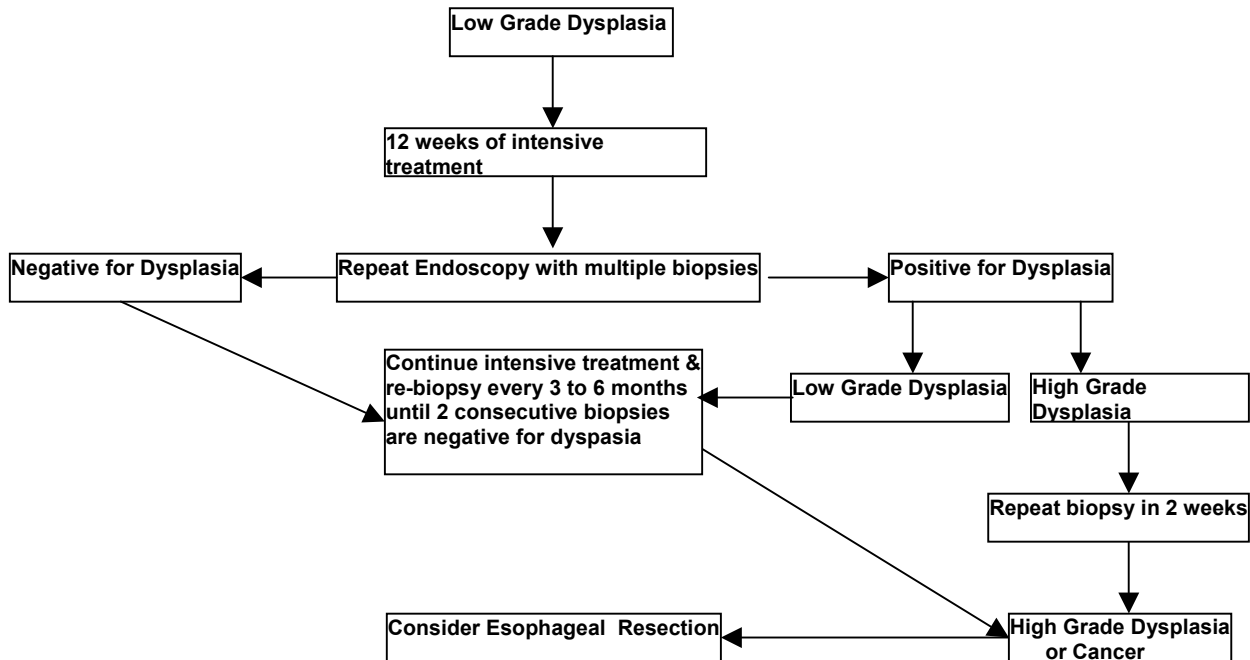
- **Epidemiology:**
 - 7% of US population have daily heartburn; 44% have heartburn monthly but only 39% mention heartburn to their doctors.
 - 40% of patients with daily heartburn have reflux esophagitis on endoscopy.
 - 18% of US population self treat with antacids more than twice weekly.
- **Symptomatology** (See Table 1)
 - “Heartburn” has a predictive value of 59% for reflux esophagitis by endoscopy & a 97% predictive value for esophageal reflux documented by pH monitoring.
 - The symptom of **regurgitation** is 66% predictive for endoscopic evidence of esophagitis.
 - **Etiologic Considerations:**
 - There are factors **intrinsic** to esophageal function that differ among patients, predisposing to GERD:
 - Lower esophageal sphincter (LES) resting pressure less than 10 mm Hg.
 - Increased frequency of transient lower esophageal relaxations (TLESRs).
 - Defective neural suppression of TLESRs when lying in the supine position.
 - Poor acid clearance because of decreased peristalsis and decreased saliva production. (As in Parkinson’s Disease or sicca syndrome.)

Table 2: Drugs and Foods Affecting LES Pressure

	Increases LES Pressure	Decreases LES Pressure
Drugs	α adrenergic agonists Antacids β blockers Cholinergics Domperidone Metaclopramide	Anticholinergics Barbiturates Benzodiazepines Calcium channel blockers Caffeine Dopamine Estrogens Nicotine Opiates Progesterone Theophyllin
Foods	Protein	Chocolate Coffee Ethanol Fat Peppermint Spearmint High fiber diet

- There are also **extrinsic** factors that predispose to GERD.
 - Anatomic abnormalities of the angle of His or the crural diaphragm.
 - Increased intra-abdominal pressure.
 - Excessive gastric filling.
 - Decreased gastric emptying.
 - Various drugs & foods lower LES resting pressure & predispose to GERD. Table 2 is a list of such substances along with a list of substances that **increase** LES pressures & may thereby ameliorate symptoms of GERD.
- **Complications⁶:**
 - **Esophageal ulceration.** There is overall a 3% to 5% incidence of erosive esophagitis in the presence of symptoms of reflux. Erosive esophagitis is present in \approx 70% of patients who have changes of Barrett's esophagus.
 - **Barrett's Esophagitis⁷:**
 - ◆ Barrett's epithelium occurs in 4.5% to 12.4% of patients with GERD & up to 40% of patients with scleroderma esophagus. Most of those without scleroderma are alcohol drinking male smokers.
 - ◆ Barrett's epithelium contains no sensory nerve receptors so heartburn symptoms may improve as the Barrett's epithelial changes progress.
 - ◆ Five percent to ten percent of patients with Barrett's esophagitis develop adenocarcinoma of the esophagus which is preceded by dysplastic mucosal changes. (Figure 1 shows the currently recommended protocol for managing dysplastic mucosal changes)⁸.
 - ◆ Esophageal stricture occurs in 30% to 80% of patients with Barrett's esophagitis.
 - **Esophageal hemorrhage:**
 - ◆ 1% of patients with reflux esophagitis hemorrhage & 10% of UGI hemorrhagic events are esophageal in origin.
 - ◆ Hemorrhage occurs most commonly in patients with Barrett's esophagus and NSAID users & is a frequent cause of death in neurologically impaired patients.
 - **Esophageal Stricture:**
 - ◆ Occurs overall in about 1% of patients with GERD.
 - ◆ Yet 25% to 30% of those with esophageal strictures have neither heartburn nor regurgitation.
 - ◆ Dysphagia (the sensation that "something gets stuck") occurs when luminal diameters decrease to less than 14 mm.
 - **Esophageal Cancer** is the reason for screening GERD patients with EGD since 86% occur in patients who develop Barrett's epithelium & dysplastic endothelial changes precede the neoplastic changes. The current management protocol for those with low grade dysplasia is shown on the next page in Figure1:
 - **Asthma:**
 - ◆ Osler in 1892 noted "risk of asthma with an overfilled stomach".
 - ◆ β adrenergics and theophyllin lower LES pressure and make reflux worse in such patients.
 - ◆ Reflux causes bronchospasm by two mechanisms:
 - Nocturnal aspiration of gastric contents
 - Vagus mediated bronchospasm occurs synchronously with any significant pH drop at the LES in 17% of asthmatics.
 - ◆ Twenty-four hour pH monitoring with patient event log is the diagnostic "gold standard" for GERD related asthma.

Figure 1: Management Protocol for Low Grade Dysplasia⁷



▪ **TREATMENT of GERD⁸:**

• **Medical Management:**

- ◆ The *sine qua non* of medical management in “garden-variety” GERD is **gastric acid control**.
 - Antacids resolve endoscopic evidence of reflux esophagitis in only 26% of cases after 30 days of treatment.
 - H₂ antagonists can be used to successfully manage symptomatic GERD with EGD documented esophagitis about 64% of the time when used at high dosage (i.e., 1.2 gms cimetidine, 600 mg ranitidine, etc.)
 - Sucralfate resolves reflux esophagitis in 68%.
 - Omiprazol 20 mg daily & other proton pump inhibitors are the mainstay of treatment for they resolve erosive esophagitis in 85%-95% of cases within 30 days.
- ◆ **Bile Reflux Esophagitis⁹** can produce a serious & debilitating form of reflux disease in patients with gastric dysmotility conditions & those whose gastric anatomy has been altered by previous surgeries. Treatment is aimed at neutralization of the alkaline bile acids with cholestyramine, aluminum hydroxide or sucralfate. **Sucralfate** is probably the optimal drug because it also binds to & protects the inflamed mucosal surface as well.
- ◆ **Prokinetic agents¹⁰** may be used for adjunctive purposes in those 24% of patients whose symptoms are not adequately controlled by gastric acid suppression. All prokinetic agents have significant side effects so they should not be prescribed routinely.
 - **Metoclopramide** increases LES pressure, and enhances gastric emptying but it also may cause Parkinsonlike side-effect in up to 20% of patients because of CNS Dopamine antagonism.
 - **Bethanechol** increases LES pressure and stimulates acid secretion. Benefits are limited by cholinergic side-effects.
 - **Cisapride** is the most effective of the prokinetic agents. It increases LES pressure, increases gastric motility and increases esophageal acid clearance via releasing acetyl choline. Unfortunately it also prolongs the QT interval of the EKG tracings of predisposed patients & was associated with several deaths among patients concomitantly taking antihistamines. It is still FDA approved but the manufacturer strictly limits its distribution to special circumstances.

- **Domperidone** is another dopamine antagonist. It does not cross the blood brain barrier so it's less likely to cause Parkinsonism but it also increases the QT interval. It is less effective than metoclopramide.
- **Surgical Management¹¹:**
 - ◆ About 5% to 10% of GERD patients require surgery for adequate symptomatic control or for other indications.
 - ◆ The **goal** of surgical intervention is to restore the anatomical reflux barrier, so interoperative monitoring of resting and contracting LES pressures is useful to predict operative success.
 - ◆ **Indications:**
 - Repeated aspiration or asthma.
 - Hemorrhagic esophagitis.
 - To prevent stricture.
 - Failure of intensive medical management, especially in patients with preserved gastric motility & persistently low LES pressures..
 - ◆ Four **procedures** have been used in recent years. The laparoscopic Nissen fundoplication has gained recent popularity because of the ease, safety & convenience with which it can be performed. Other procedures include the following:
 - Belsey Mark IV invagination procedure.
 - Conventional open Nissen Fundoplication {more recently performed laparoscopically}.
 - Hill posterior gastropexy.
 - Angelchik prosthesis.
 - ◆ **Surgical Outcomes:**
 - The conventional Nissen and Hill procedures produce equally good results in experienced hands but the lapaoscopic Nissen procedure is unparalleled for ease, convenience & safety. All should produce good to excellent results in ≈ 80% of cases with a 10 year failure rate <10%.. Nissen fundoplication produces an uncomfortable inability to belch in ±20% of cases.
 - The Angelchik prosthesis is a doughnut shaped ring which was sewn to the gastric fundus. It is no longer used because of migration of the prosthesis over the stomach wall & within the abdominal cavity sometimes with serious complications. Older patients may still have this prosthesis in place however.

VII SCLERODERMA ESOPHAGUS¹²:

- **Definition:** Scleroderma or Systemic Sclerosis as it is now called is a collagen vascular disease featuring an inflammatory overstimulation of subcutaneous collagen & other matrix proteins resulting in thickening of the skin, replacement of elastic fibrils & smooth muscle cells in the skin & sometimes the esophagus, the heart & lungs & the kidneys.
- **Esophageal changes** consist of atrophy & loss of smooth muscle in the distal 1/3 of the esophagus resulting in lower than normal resting LES pressures but normal relaxation upon swallowing The LES & distal esophagus may become patulous useless in preventing reflux while lying flat.
- **Diagnosis:** The diagnosis of scleroderma based on the presence of it's one major criteria or 2 of the minor criteria is 91% sensitive & 97% specific for the disease. Diagnostic criteria are shown in Table 3. Having said that however, there is another form of systemic scleroderma that does not manifest skin changes but may involve the viscera. That type is called "*Systemic Sclerosis sine Scleroderma*". Other collagen vascular diseases can produce a similar picture.

Table 3: Diagnostic Criteria for Scleroderma (Systemic Sclerosis) *

Major Criterion	Minor Criteria
Bilateral symmetrical dermal thickening of the Proximal extremities, face, neck or trunk	Sclerodactyly Digital pitting scars or loss of tissue on the volar finger tips Bibasilar Pulmonary Fibrosis

*One major or 2 minor criteria needed for diagnosis

- **Treatment:** Because the incidence of erosive esophagitis, Barrett's endothelial changes, stricture & carcinoma are increased secondary to the reflux, vigorous treatment with proton pump inhibitors & careful clinical surveillance for GERD & its complications are indicated.

VIII ACHALASIA⁵:

- **Definition:** Primary idiopathic achalasia is a neuromuscular disorder in which there is a progressive loss of inhibitory neurons from the esophageal myenteric plexus resulting in nonperistaltic esophageal contractions that produce chest pain early in the course & failure of relaxation of the LES later, producing dysphagia, regurgitation & sometimes aspiration of liquids & solids.
- **Epidemiology:** The gender ratio is equal in men & women. The population prevalence is about 7 to 13/100,000, & the annual incidence of newly diagnosed cases about 0.5/100,000.
- **Typical Symptoms** include the early appearance of noncardiac chest pain that may mimic angina pectoris in that it may be precipitated &/or worsened by emotional stress. Later there occurs intermittent, slowly progressive dysphasia for solids and liquids that is localized to the xiphoid area. Later yet regurgitation of stagnant undigested food begins occurring at night. On average, symptoms are present an about seven years before the diagnosis is made.
- **Pathogenesis:**
 - **Primary Idiopathic Achalasia:** Inhibitory neurons containing vasoactive intestinal peptide (VIP) & nitric oxide are lost from the myenteric plexus & degenerative changes also occur in the vagus nerve & the swallowing center in the midbrain producing LES hypertonicity & failure of relaxation. Chronic obstruction of the distal esophagus coupled with the loss of neurons aggravates the swallowing difficulty & eventually produces aperistalsis. The persistent obstruction with aperistalsis produces esophageal dilatation which further weakens peristalsis.
 - **Secondary Achalasia** may occur as a post surgical complication after one of the fundoplication procedures & is one of the more common (albeit rare) complications of the Nissen fundoplasty. Infiltrative gastric malignancies are the cause of achalasia in 4% of all cases. They include gastric & esophageal carcinomas & lymphomas. Chronic idiopathic intestinal pseudo-obstruction (Ogilvie's syndrome) may produce a similar picture. Eosinophilic gastroenteritis & Chagas disease are 2 other "zebras".
 - **Complications:**
 - Esophagitis secondary to candida albicans or from stasis with or without failure to clear alcohol or pills (especially NSAIDs).
 - Epiphrenic pulsion diverticula.
 - Esophageal cancer occurs in 3.5%. The duration of symptoms of achalasia before the cancer is found is about 22 years. The average age of the patient is 48 years at diagnosis.
 - **Treatment:**
 - Pharmacological Treatments:
 - ◆ Nitroglycerine 0.4mg or 0.6mg administered sublingually as needed for chest pain & if given before meals may ameliorate the dysphagia.
 - ◆ Isosorbide dinitrate 2.5mg to 5mg sublingually or 10 to 20mg orally can be used in the same manner.
 - ◆ The side effects of NTG & isosorbide include headache & postural hypotension. They are more frequently effective than nifedipine but more likely to cause side effects.
 - ◆ Nifedipine 60-90 mg QID relieves symptoms and lowers LES pressure about 50% of the time.
 - Endoscopic Treatments:
 - ◆ Bougienage doesn't work, is dangerous & shouldn't be attempted in achalasia.
 - ◆ Pneumatic dilatation is the most effective nonsurgical therapy but is contraindicated with epiphrenic diverticula, prior esophageal perforation, adjacent aortic aneurysms or active esophagitis. Success rates are 60% to 85%. Esophageal perforation or other major complications occur in about 4.5% of cases with an operative mortality of about 0.2%.
 - Surgical Interventions:
 - ◆ The Modified Heller esophagomyotomy produces good to excellent results in 82% of patients.
 - ◆ The rate of postop reflux esophagitis is 11%.
 - ◆ The rate of operative failure requiring reoperation is 6.2%.
 - **Prognosis:**
 - Primary idiopathic achalasia is an uncomfortable but indolent chronic condition which doesn't shorten life span. Mean age at death 80.5 years.

IX DIFFUSE ESOPHAGEAL SPASM (DES)^{4,9} & its variants produce 10% of all cases of noncardiac chest pain.

- **Symptoms:**
 - Spontaneous pressure like noncardiac chest pain with or without radiation that may not be clinically distinguishable from angina pectoris or achylasia.
 - Occasional syncope occurs secondary to vasovagal bradyarrhythmias.
 - Dysphagia is common.
- **Types of DES:**
 - Differentiation of the specific type of esophageal spasm is made by manometry.
 - **Classical DES** demonstrates spontaneous simultaneous nonperistaltic esophageal contractions more than 30% of the time that can be reproduced by edrophonium in 23% of cases.
 - Patients with DES sequential contractions may be replaced by uncoordinated nonperistaltic contractions that produce the appearance of curling. This variant is called “**corkscrew esophagus**”.
 - Patients with **Nutcracker Esophagus** have peristaltic contractions that differ from normal only by their amplitude & strength of contraction. The hypercontractions most often occur after the onset of chest pain during ambulatory monitoring studies. This suggests that the “nutcracker” phenomenon may be an epiphenomenon. Nutcracker patients score high on anxiety and somatization scales & 56% of nutcracker patients also have irritable bowel syndrome compared with 28% on controls
- **Etiology:**
 - Patchy degeneration of neuronal processes but not the neuronal cell bodies is common & in such cases the disease may progress to achylasia.
 - In addition however many patients with motility disorders are persistently anxious & live “compromised lifestyles”. In these patients anxiety and somatization scale scores are increased & 80% have specific psychiatric diagnoses.
 - Most have diminished pain threshold to esophageal pressure as measure by balloon manometry.
- **Diagnosis:**
 - Delineation of the specific type of esophageal dysfunction is made by manometry.
 - 34% of the time the symptom may be reproduced by edrophonium challenge.
- **Treatment:**
 - Both nifedipine and long acting nitrates lower esophageal pressures but double blind trials show no difference from placebo in symptom relief.
 - Trazodone 150 mg/d has been shown significantly better than placebo for symptom relief.
 - Esophageal dilatation, pneumatic dilatation and “long” Hiller esophagomyotomy have all been used with controversial results (A Mayo Clinic study reported 70% success rate after surgery.)

X GLOBUS HYSTERICUS¹³:

- **The Symptom:**
 - “Globus” is the symptom of a “lump in the throat that won’t go down”. Globus hystericus is that symptom when it occurs in response to an emotionally charged life event. Globus hystericus may be accompanied by aphonia or the sensation of choking or smothering. Although the subjective sensation of “difficulty swallowing” may be present, the swallowing mechanism is in fact intact.
 - Globus hystericus is a very common symptom that reportedly occurs from time to time in about 45% of the general population. In its more severe or persistent form, it is the psychiatric condition most often referred for otolaryngological consultation (≈ 4% & 13% of ENT referrals).
- **Etiology:**
 - Globus hystericus is a “conversion” symptom, a type of “somatoform disorder”, which means that it is not consciously controlled, but is instead, an involuntary bodily response, usually to a life event that the patient finds difficult to accept (symbolically reflected as “difficult to swallow”).
- **Differential Diagnosis:**
 - The organic condition most frequently misdiagnosed as globus hystericus is DES or one of its variants (≈80%), but GERD, achalasia, other neuromuscular disorders & obstructive conditions (including esophageal cancer) present at first as globus. Most of these other conditions can be suspected by the presence of other symptoms, but even if other symptoms are absent, the alternative diagnoses should be excluded by appropriate testing in those patients in whom the symptom of globus persists.
 - In new onset globus it is important to explore & document all aspects of the patient’s social history as positive support for the diagnosis of globus hystericus as well as the absence of symptoms suggestive of other organic causes.

- **Treatment:**
 - There are no controlled trials available, so the specific treatment depends on clinical judgment. It is important first of all however, to exclude organic causes, to establish the psychological rationale for the diagnosis & to reassure & support the patient.
 - With recent onset globus, my personal management depends on the associated symptoms. When it is associated with depression or anxiety, an SSRI may be indicated. Benzodiazepines should usually be avoided because of their addictive potential as well as their known hazards in elderly & cognitively impaired patients. None the less, a short course (< 2 weeks) of low dose ($\approx 0.125\text{mg t. i. d.}$) of alprazolam (Xanax[®]) may be helpful during the time interval before the SSRI takes effect .
 - When the symptom persists for more than 2 weeks or there is no obvious precipitating interpersonal or situational cause, an organic cause should be excluded by appropriate tests.

XI REFERENCES:

-
- ¹ Rothstein RD, Ouyang A: Chest pain of esophageal origin. *Gastroenterol Clin N Amer* 1989;**18**:257-74.
 - ² Traube M: The spectrum of symptoms and presentation of gastroesophageal reflux disease. *Gastroenterol Clin N Amer* 1990;**19**(3):609-16.
 - ³ Sontag SJ: The medical management of reflux esophagitis: Role of antacids and acid inhibitors. *Gastroenterol Clin N Amer* 1990;**19**:683-712..
 - ⁴ Richter JE, Bradley LA, Castell DO: Esophageal chest pain: Current controversies in pathogenesis, diagnosis and therapy. *Ann Int Med* 1989;**110**:66-78.
 - ⁵ Reynolds JC, Parkman HP: Achalasia. *Gastroenterol Clin N Amer* 1989;**18**:223-255.
 - ⁶ Kozarek RA: Complications of reflux esophagitis and their medical management. *Gastroenterol Clin N Amer* 1990;**19**:713-732.
 - ⁷ Polepalle SC, McCallum RW: Barrett's esophagus: Current assessment and future perspectives. *Gastroenterol Clin N Amer* 1990;**19**:733-45.
 - ⁸ Ogorek CP, Fisher RS: Detection and treatment of gastroesophageal reflux disease. *Gastroenterol Clin N Amer* 1989;**18**:293-313.
 - ⁹ Goyal RK, Diseases of the Esophagus. Chapter 273 in *Harrison's Principles of Internal Medicine* 16thEdition. Editors: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL. McGraw-Hill NY,NY 2005 Pages 1739-46.
 - ¹⁰ Reynolds JC: Prokinetic agents: A key in the future of gastroenterology. *Gastroenterol Clin N Amer* 1989;**18**:437-458.
 - ¹¹ Decktor DL, Robinson MG: Gastroesophageal reflux: Clinical diagnosis, current therapy, future trends. *Hepato-gastroenterol* 1990;**30** (Suppl 1):11-17.
 - ¹² Gilliland BC, Systemic Sclerosis (Scleroderma) & Related Disorders. Chapter 303 in *Harrison's Principles of Internal Medicine* 16thEdition. Editors: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL. McGraw-Hill NY,NY 2005 Pages 1979-90.
 - ¹³ Finkenbine R, Meile VI, Globus Hystericus: A brief review. *Gen Hosp Psych*. 2004;**26**:78-83.