

Original Article

Clinical Practice Guidelines for the Assessment of Uninvestigated Esophageal Dysphagia

Louis WC. Liu,^{*} Christopher N. Andrews,[†] David Armstrong,[§] Nicholas Diamant,^{||} Nasir Jaffer,[¶] Adriana Lazarescu,[#] Marilyn Li,^{||} Rosemary Martino,^{**} William Paterson,^{||} Grigorios I. Leontiadis,[§] Frances Tse[§]

^{*}Division of Gastroenterology, Department of Medicine, University of Toronto, Toronto, ON [†]Division of Gastroenterology, Department of Medicine, University of Calgary, Calgary, AB [§]Department of Medicine, McMaster University, Hamilton, ON ^{||}Division of Gastroenterology, Department of Medicine, Queen's University, Kingston, ON [¶]Department of Medical Imaging, Mount Sinai Hospital, Toronto, ON [#]Division of Gastroenterology, University of Alberta, Edmonton, AB ^{**}Department of Speech-Language Pathology, University of Toronto, Toronto, ON

Correspondence: Louis Liu, BEng, MEng, PhD, MD, FRCPC, University of Toronto Toronto Western Hospital, University Health Network 399 Bathurst Street, Main Pavilion 8th Floor, Room 329 Toronto, ON, Canada M5T 2S8, e-mail louis.liu@uhn.ca

Abstract

Background and aims: Our aim is to review the literature and provide guidelines for the assessment of uninvestigated dysphagia.

Methods: A systematic literature search identified studies on dysphagia. The quality of evidence and strength of recommendations were rated according to the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach. Statements were discussed and revised via small group meetings, teleconferences, and a web-based platform until consensus was reached by the full group.

Results: The consensus includes 13 statements focused on the role of strategies for the assessment of esophageal dysphagia. In patients presenting with dysphagia, oropharyngeal dysphagia should be identified promptly because of the risk of aspiration. For patients with esophageal dysphagia, history can be used to help differentiate structural from motility disorders and to elicit alarm features. An empiric trial of proton pump inhibitor therapy should be limited to four weeks in patients with esophageal dysphagia who have reflux symptoms and no additional alarm features. For patients with persistent dysphagia, endoscopy, including esophageal biopsy, was recommended over barium esophagram for the assessment of structural and mucosal esophageal disease. Barium esophagram may be useful when the availability of endoscopy is limited. Esophageal manometry was recommended for diagnosis of esophageal motility disorders, and high-resolution was recommended over conventional manometry.

Abbreviations:

AGA,	American Gastroenterological Association;	HREM,	high resolution esophageal manometry;
ACG,	American College of Gastroenterology;	IEM,	ineffective esophageal motility;
CAG,	Canadian Association of Gastroenterology;	LES,	lower esophageal sphincter;
CI,	confidence interval;	OR,	odds ratio;
CPG,	clinical practice guideline;	RCT,	randomized controlled trial;
EGJ,	esophagogastric junction	RR,	relative risk;
EGD	endoscopy;	SWAL-QOL,	swallowing quality of life scale;
EoE,	eosinophilic esophagitis;	TOR-BSST [®] ,	Toronto bedside swallowing screening test;
GRADE,	Grading of Recommendation Assessment, Development and Evaluation;	V-VST,	viscosity swallowing test;
HR,	hazard ratio;	WGO,	World Gastroenterology Organisation;
		WVQ,	wet voice quality

Conclusions: Once oropharyngeal dysphagia is ruled out, patients with symptoms of esophageal dysphagia should be assessed by history and physical examination, followed by endoscopy to identify structural and inflammatory lesions. If these are ruled out, then manometry is recommended for the diagnosis of esophageal dysmotility.

Keywords: *deglutition; swallowing; gastroesophageal reflux disease (GERD)*

INTRODUCTION

Dysphagia is a common condition affecting about 3% of the adult population (1). It is usually sub-classified into oropharyngeal dysphagia (affecting the mouth and pharynx) and esophageal dysphagia (affecting the esophageal body and esophagogastric junction) (2, 3). Oropharyngeal dysphagia has been described as difficulty initiating a swallow or passing food through the mouth or throat, while esophageal dysphagia is characterized by difficulty transporting material down the esophagus (2). Esophageal dysphagia is usually the result of either structural or inflammatory abnormalities such as strictures, rings, webs, malignancy or esophagitis (e.g., reflux esophagitis or eosinophilic esophagitis, EoE) (4–7), or motility disorders such as achalasia, ineffective esophageal motility (IEM), esophageal spasm or esophagogastric junction (EGJ) outflow obstruction (8–10).

The most recent guidelines on the diagnosis and management of dysphagia from the World Gastroenterology Organization (WGO), provide a practical approach but they did not systematically evaluate the evidence (2). Furthermore, the most recent Canadian guideline for the evaluation of dysphagia was published in 1998 (3).

This consensus guideline was developed using the stringent GRADE (Grading of Recommendation Assessment, Development and Evaluation) method (11) to evaluate the evidence, in order to provide updated evidence-based guidelines for the assessment of uninvestigated dysphagia. This consensus focused on esophageal dysphagia, which accounts for the majority of cases in the general population (1, 4). It is assumed that recommended procedures are conducted by appropriately trained and experienced clinicians, in order to achieve the diagnostic yields suggested by the literature.

METHODS

Scope and Purpose

Participants identified six major topics and discussed 26 specific questions pertaining to the diagnosis of dysphagia. The guideline process was initiated in July 2012 (the consensus group met in a series of teleconferences between September 2013 and February 2015). The process was completed, via discussions by telephone and in person, and through the CAG online platform (see below), without a face-to-face consensus

meeting. This process resulted in the 13 statements that were voted on by the members of the committee and are presented in this manuscript. The final document was approved by each member of the consensus group.

Sources and Searches

The consensus group performed a systematic literature search of MEDLINE (from 1946 onward), EMBASE (from 1980 onward), and CENTRAL (Cochrane Central Register of Controlled Trials) up to October 2012, which was subsequently updated to March 2015. Key search terms were deglutition, dysphagia, swallowing, esophagus, oropharyngeal, motility disorders, barium, endoscopy, endosonography, biopsy, gastroesophageal reflux disease (GERD), proton pump inhibitors (PPI), and manometry. The search was limited to human studies and the English language. The strategies used are detailed further in Appendix 1. The searches yielded 11,781 papers, of which the abstracts (when available) were reviewed by two independent committee members assigned to each section, with conflicts resolved by consensus. This resulted in 635 papers being selected for full text review.

Review and Grading of Evidence

Overall quality of evidence for individual statements was assessed using the GRADE method (11) by two non-voting methodologists (GL and FT). QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) was used to assess the quality of diagnostic accuracy studies (12). The quality of evidence for each statement was graded as high, moderate, low or very low, as described in GRADE (11, 13) and prior CAG consensus documents (14, 15).

Approved product labeling from government regulatory agencies varies from country to country, and while not ignored, recommendations are based on evidence from the literature and consensus discussion, and may not fully reflect the product labeling for a given country.

Consensus Process

The consensus group consisted of nine voting members (eight participants and one chair, LL), including seven gastroenterologists, one speech language pathologist (RM) and one radiologist (NJ) from Canada with expertise in the management of dysphagia.

The CAG facilitated the consensus process via small group meetings, teleconferences and a web-based consensus platform (ECD solutions, Atlanta, Georgia, USA) until consensus on the statements was reached by the full group. The consensus group developed the initial statements, reviewed the results of the literature search (with each article being reviewed by at least two group members) through the web-based platform, and then ‘tagged’ (selected and linked) references deemed relevant to a specific statement. All consensus group members were provided with access to copies of ‘tagged’ references. Using a modified Delphi process (16, 17), anonymous voting was then conducted by participants to determine their level of agreement with the individual statements. The statements were revised via teleconference and emails through three iterations, with accompanying online voting. A statement was accepted if >75% of participants voted five (agree with minor reservation) or six (agree strongly) on a scale of one to six (with one, two, three, and four being disagree strongly, disagree with major reservation, disagree with minor reservation and agree with major reservation, respectively). On the third vote, participants voted on the ‘strength’ of the recommendation, which was accepted with a 51% vote. Consistent with the GRADE system, the strength of each recommendation was classified as strong (“we recommend . . .”) or conditional (“we suggest . . .”). The strength of the recommendation considers risk-benefit balance, patients’ values and preferences, cost and resource allocation, and the quality of the evidence. Therefore, it is possible for a recommendation to be classified as ‘strong’ despite having low-quality evidence to support it, or ‘conditional’ despite the existence of high-quality evidence to support it (18). Based on the GRADE approach, a strong recommendation indicates the statement should be applied in most cases, while a conditional recommendation signifies that clinicians “should recognize that different choices will be appropriate for different patients and that they must help each patient to arrive at a management decision consistent with her or his values and preferences” (18).

The initial manuscript was drafted by the meeting chair, revised and approved by all members of the consensus group, and then made available to all CAG members for comments before submission for publication. As per CAG policy, all participants provided written disclosure of potential conflicts of interest for the 24 months prior to the meeting, which were made available to the other group members.

RECOMMENDATION STATEMENTS

Section 1: Identifying Oropharyngeal Dysphagia in Patients Presenting with Dysphagia

Statement 1.1: In patients presenting with dysphagia, we recommend using presenting symptoms and physical examination

as the initial assessment to identify patients with oropharyngeal dysphagia.

- GRADE: Strong recommendation, very low-quality evidence. Vote: agree strongly, 78%; agree with minor reservation, 11%; agree with major reservation, 11%

Statement 1.2: In patients presenting with dysphagia, we recommend prompt identification of those with oropharyngeal dysphagia because of the increased risk of aspiration.

- GRADE: Strong recommendation, low-quality evidence. Vote: agree strongly, 100%

Dysphagia is the sensation that foods and/or liquids are being obstructed or hindered in their passage from the mouth to the stomach. Oropharyngeal dysphagia is described as difficulty initiating a swallow or passing food through the region of the mouth or throat; whereas, esophageal dysphagia refers to difficulty in transferring material down the esophagus in the retrosternal region (2).

Patients with certain diseases or disorders are at increased risk of oropharyngeal dysphagia and a diagnosis of these conditions should direct attention to the possibility of its presence. Some conditions such as stroke; head and neck cancer; surgery to the head, neck or cervical spine; abnormality of cervical spine, (e.g., osteophytes); and abnormality of cranial nerves 5, 7, 9, 10, 11 or 12 are associated with an increased risk of oropharyngeal dysphagia (19). Hence, the presence of these conditions should direct attention to the possible presence of oropharyngeal dysphagia. Oropharyngeal and esophageal dysphagia can occur together in conditions such as progressive neurological disorders (e.g., Parkinson’s disease, myotonic dystrophies), infective disorders (e.g., candida); and collagen vascular disorders (20).

Studies also suggest that patients are more accurate when subjectively localizing lesions in the distal rather than the proximal esophagus (21–24). In a prospective radiographic study of 130 patients, 26 were found to have a lower esophageal mucosal ring; 16 (62%) of whom demonstrated marshmallow impaction at the ring, and of these, 12 experienced dysphagia during the study. Of these 12, seven (84%) subjectively reported perceiving bolus sticking in the neck during the radiographic study where no structural pharyngeal or cervical esophagus abnormality was found (21). In another prospective study in 139 patients with dysphagia and an esophageal stricture, 22% of patients localized the level of obstruction exactly, 52% were within +/- 2 cm, and 74% within +/- 4 cm (24). Distal lesions were localized proximally by 15% of patients, but proximal lesions were only localized to the distal esophagus by 5% of patients (24).

The consensus group concluded that when patients indicate that the food is sticking in the retrosternal region, it is likely to be caused by esophageal dysphagia. However, when the patient localizes dysphagia to the sternal notch or the throat, this is unreliable. Because of the increased risk of aspiration, we

recommend patients first be investigated for potential oropharyngeal dysphagia.

Although there are no clinical assessment tools that can help differentiate oropharyngeal from esophageal dysphagia, a higher score on the Eating Assessment Tool (EAT) (25) is associated with a higher risk of aspiration in patients presenting with dysphagia (26). In addition, higher scores on the dysphagia-related swallowing quality of life scale (SWAL-QOL) can identify patients with oropharyngeal dysphagia (27). Wet voice quality (WVQ) is frequently used in clinical settings but does not appear to be a reliable indicator of oropharyngeal dysphagia (28). Bedside swallowing tests have been developed to screen for oropharyngeal dysphagia. A systematic review of these tests (29) identified four tests with sensitivity of $\geq 70\%$ and specificity of $\geq 60\%$, including the Toronto bedside swallowing screening test (TOR-BSST[®]) (30), the volume-viscosity swallowing test (V-VST) (31), the 3-ounce water swallow test (32), and the cough test (33). In neurological patients, these tests have demonstrated utility in identifying oropharyngeal dysphagia (30, 31) and risk of aspiration (32, 33). A prospective, observational study found a significantly lower rate of pneumonia at institutions that used a formal dysphagia screening protocol compared with those that did not (2.4% versus 5.4%; $P = 0.0016$). This remained significant even after adjusting for stroke severity. However, this study was judged at high risk of bias, since sites with a protocol may have had other characteristics that also had an impact on the development of pneumonia (34). In addition, these tests were not used to differentiate between oropharyngeal and esophageal dysphagia in these studies.

Oropharyngeal dysphagia is associated with high risk of aspiration (26). A history of dysphagia and aspiration increases the risk of pneumonia (35, 36). A systematic review of observational studies in stroke patients reported that dysphagia was associated with an increased risk for pneumonia (RR, 3.17; 95% CI, 2.07–4.87) and an even greater risk for aspiration (RR, 11.56; 95% CI, 3.36–39.77) (35). In a case-control study, elderly patients with oropharyngeal dysphagia had a 12-times greater risk of community-acquired pneumonia (odds ratio [OR], 11.9; 95% CI, 3.03–46.9) compared to those without oropharyngeal dysphagia, in a multivariate analysis that controlled for comorbidities and functionality (36).

The consensus group concluded that available tools, including patient-reported symptoms, physical examination, and bedside screening tests should be used to help identify cases of oropharyngeal dysphagia because of the high risk of aspiration and pneumonia. If oropharyngeal dysphagia is suspected, a referral to a speech language pathologist, or other appropriate specialist, for a clinical assessment (e.g., videofluoroscopic swallowing study) is recommended to confirm the diagnosis and guide management (37).

Section 2: Role of History and Physical Examination in the Assessment of Esophageal Dysphagia

Statement 2.1: In patients with esophageal dysphagia, we recommend history be used to help differentiate structural and motility disorders of the esophagus.

- GRADE: Strong recommendation, moderate quality evidence. Vote: agree strongly, 56%; agree with minor reservation, 33%; disagree with minor reservation, 11%

In observational studies the most common diagnosis in patients with dysphagia was GERD, accounting for about 17% to 28% of cases (4–7). Other less common diagnoses include inflammatory esophagitis (e.g., EoE, upper GI Crohn's disease), infectious esophagitis, strictures, rings, webs, esophageal cancer and motility disorders (4–7).

Some signs and symptoms have been reported to be associated with structural versus motility disorders (Table 1). In a prospective cohort study, malignancy was more common in patients with shorter duration of dysphagia, while peptic stricture was more frequent in those with longer duration of symptoms (38). There was no difference in the likelihood of malignancy based on the level of dysphagia (pharyngeal level dysphagia 11.9% versus mid-sternal or lower sternal dysphagia 12.4%; $P = \text{NS}$). The strongest predictor of malignancy was duration of dysphagia (< 8 weeks versus > 26 weeks: OR, 11.02; 95% CI, 4.90–24.80; $P < 0.0001$) (38).

Patients with dysphagia associated with achalasia or esophageal spasm frequently experience symptoms over years including regurgitation, chest pain and weight loss (39–43). Case series have reported that patients with a lower esophageal muscular ring (44), or a Schatzki ring (45), can exhibit features of a 'motility-like' condition and experience a long duration of intermittent, non-progressive solid dysphagia.

Conditions such as autoimmune (e.g., lupus, 63–72%) and connective tissue diseases (88%) are frequently associated

Table 1. Presenting history and symptoms suggestive of structural and motility disorders^{38, 46, 113}

	Structural disorders	Motility disorder
Symptoms	<ul style="list-style-type: none"> • Regular • Short duration, rapid progression • Solid (may progress to liquid) 	<ul style="list-style-type: none"> • Intermittent • Long duration • Solid and liquid
History	<ul style="list-style-type: none"> • Alarm features <ul style="list-style-type: none"> ◦ Onset age > 50 y ◦ Bleeding ◦ Odynophagia ◦ Weight loss ◦ Vomiting 	<ul style="list-style-type: none"> • Connective tissue diseases • Diabetes mellitus • Non-cardiac chest pain

with esophageal hypomotility; therefore, dysphagia in these patients suggests an esophageal motility disorder (46). EoE is a frequent diagnosis among patients with dysphagia (33–35%) and is more common in patients with a history of food allergies (36.8% versus 9.3%, $P < 0.001$) or asthma (22% versus 9%, $P < 0.01$) compared to those without (47–49).

The consensus group concluded that while there may be some distinguishing clinical features among patients with dysphagia of different etiologies, a standard strategy for investigations should be pursued in all cases, regardless of whether the symptoms suggest a structural or a motility cause. In most circumstances, initial assessment will be conducted to first rule out structural and inflammatory lesions (endoscopy [EGD] and/or barium esophagram), followed by assessment of motility (manometry) if no clear structural or inflammatory lesions has been identified.

Statement 2.2: In patients with esophageal dysphagia, we recommend history and physical examination, including assessment of other alarm features that require urgent investigations to ensure timely referral for appropriate management.

- GRADE: Strong recommendation, low-quality evidence.

Vote: agree strongly, 78%; agree with major reservation, 22%
In Canada, the estimated 2017 incidence of new cancer cases was 103,100 cases among males and 103,200 among women. Among these newly diagnosed cancers, esophageal cancer was found to affect 1.7% of men (1,800 cases) and 0.5% of women (530 cases) (50). Among individuals with dysphagia, the rate of esophageal cancer was 5.9% in a retrospective endoscopy database cohort (4), but only 0.6% in a cross-sectional, general population-based cohort (1).

Alarm features, including vomiting, gastrointestinal bleeding, abdominal mass, dysphagia, unexplained weight loss and anemia, have been associated with increased risks of serious diagnoses, including esophageal and other gastric cancers (6, 51–54). Since the risk of esophageal cancers increases with age (50, 55), patients whose age is over 50–55 years is generally also considered as an alarm feature (6, 53, 56).

Almost 60% of patients with dysphagia had additional alarm symptoms, including weight loss (15%), vomiting (15%) and anemia (3.6%) (6). The combination of dysphagia with an additional alarm feature (especially age > 50 years and weight loss) was associated with a significantly increased risk of esophageal cancer (6, 56, 57).

Canadian consensus guidelines on wait times recommended that patients with severe or rapidly progressive dysphagia, or a high likelihood of cancer, be assessed within two weeks (58).

This consensus group concluded that patients with esophageal dysphagia should be assessed for the presence of additional alarm features associated with disorders that have a high risk for poor outcomes, such as GI cancers, so that the appropriate investigations (e.g., endoscopy or imaging studies) can be conducted within the recommended wait time.

Section 3: Role of Barium Contrast Studies in the Evaluation of Esophageal Dysphagia

Statement 3.1: In patients with esophageal dysphagia, we recommend endoscopy over barium esophagram to improve the diagnosis of structural and mucosal esophageal disease.

- GRADE: Strong recommendation, very low-quality evidence. Vote: agree strongly, 78%; agree with minor reservation, 22%

Studies comparing the diagnostic accuracy of endoscopy and barium esophagram are mainly small and retrospective in nature (59–64). Most of these studies used barium swallow as the index test and EGD as the reference standard. However, generally EGD was interpreted with knowledge of the results of the barium swallow, and patients were not randomly selected. The results of these studies are conflicting with some reporting greater accuracy with barium esophagram (59, 63) and others with EGD (60–62, 64).

In a prospective study, including 25 patients with dysphagia, in which pathology was used as the reference standard, a correct diagnosis was made in 50% of cases based on radiology, compared to 95.5% of cases based on endoscopy. However, this study may have limited generalizability because all patients were HIV positive and over half had AIDS defining opportunistic infections (64). It should also be noted that all of the barium esophagram studies were performed before the widespread awareness of EoE. Sensitivity and specificity of esophagram for EoE is unknown, however, since biopsy is required for the diagnosis of EoE, it further underscores the advantage of endoscopy over barium studies for diagnosis of dysphagia.

A cost-analysis study found that initial barium esophagram was more costly than initial EGD with therapeutic intent (dilation) for patients with history suggesting benign obstruction ($\$602 \pm 22$ versus $\$515 \pm 5$, $P < 0.02$), but was less costly than EGD for diagnoses and treatment involving abnormal motility (for achalasia, $\$67 \pm 17$ versus $\$547 \pm 21$, $P < 0.001$) (65).

Barium esophagram may be useful as the initial test to map the esophagus when the clinician judges the patient to be at high risk of perforation on EGD, such as those with suspected high-risk lesions or strictures high up in the esophagus (66, 67). Performing both tests can provide complementary information in some situations, such as pre-operative assessment of Zenker's diverticulum (68) or the assessment of suspected achalasia if manometry is not readily available (69).

Statement 3.2: In some patients with esophageal dysphagia, we suggest a barium esophagram when there is limited local access to endoscopy to assess for significant structural lesions and facilitate timely referral to urgent endoscopy and specialist consultation.

- GRADE: Strong recommendation, very low-quality evidence. Vote: agree strongly, 78%; agree with minor reservation, 11%; agree with major reservation, 11%

Studies show that barium esophagram can be sensitive for the detection of rings (62), stenoses (63), dysmotility, hiatal hernia, benign stricture and esophagitis (59), as well as esophageal carcinoma (60). However, in one study, barium esophagram failed to identify about half of proximal stenoses or concentric rings detected on EGD (61). A prospective study, in which pathology was used as the reference standard, reported good specificity, but poor sensitivity of barium esophagram compared to EGD (64).

The consensus group concluded that although EGD is generally preferred (see statement 3.1), in areas of limited availability to EGD, barium esophagram does have diagnostic utility and can be useful in identifying patients who warrant urgent access to EGD.

Statement 3.3: In patients with esophageal dysphagia, we recommend esophageal manometry over barium esophagram to improve the diagnosis of esophageal motility disorders.

- GRADE: Strong recommendation, very low-quality evidence. Vote: agree strongly, 67%; agree with minor reservation, 33%

Prospective studies in consecutive patients (70–74) and retrospective studies (75, 76) have evaluated the diagnostic accuracy of manometry and barium esophagram in patients with dysphagia. In patients with dysphagia, and abnormal manometry studies, barium esophagram often demonstrated poor sensitivity (70, 71, 74–76). Compared to manometry, the sensitivity of barium esophagram was generally greatest for the diagnosis of achalasia, as compared with other esophageal motility disorders (71, 72, 75). In addition, sensitivity improved when nutcracker esophagus and nonspecific esophageal motor disorders were excluded (75).

In some situations, performing both tests can provide complementary information, for example, in patients with EGJ outflow obstruction (Chicago 3 classification) or post-fundoplication dysphagia, barium esophagram can complement manometry in helping to identify functional defects and guide management decisions (77). In addition, in patients with achalasia on manometry, timed barium esophagram can be used to assess the degree of impairment of esophageal emptying (78).

The consensus group agreed that, once structural and inflammatory abnormalities have been ruled out with EGD or barium esophagram, esophageal manometry should be used to assess suspected motility disorders.

Section 4: Role of Empiric Treatment with PPI in Esophageal Dysphagia

Statement 4.1: In patients under 50 years old presenting with esophageal dysphagia and reflux symptoms, and no alarm features to suggest underlying malignancy, we recommend further testing be performed if dysphagia does not resolve completely after a 4-week trial of oral proton pump inhibitor (PPI) given twice daily.

- GRADE: Strong recommendation, very low-quality evidence. Vote: agree strongly, 44%; agree with minor reservation, 66%

An empiric trial of proton pump inhibitor (PPI) therapy is a common strategy in patients presenting with dysphagia and typical GERD symptoms, such as heartburn and regurgitation (4). This strategy is justified by the high rate of GERD or esophagitis in patients with dysphagia. In retrospective database analyses, the most common findings on EGD in patients with dysphagia, were GERD/esophagitis (17%–28%), esophageal strictures (2.6%–41%) and normal esophagus (24%–32%) (4–7). In addition, PPI prescription is the most common treatment after EGD in patients with dysphagia (4), and PPIs have been shown to significantly improve symptoms of dysphagia associated with GERD (79, 80).

The main concern with a strategy of empiric PPI therapy is the potential for missed or delayed cancer diagnoses. In 2017, among Canadian adults, the estimated incidence of new esophageal cancers was 5.7/100,000 (2,300 cases), and of stomach cancers 8.6/100,000 (3,500 cases) (50). However, among patients referred for EGD for evaluation of dysphagia, the rates of esophageal cancer ranged from 3.1 to 8.1% (4–7). Cancer findings were more common in males, patients ages 50–60 years or older, and those with additional alarm features (6, 7, 56, 81).

In population-based studies, the incidence of gastroesophageal cancer was not significantly higher in users of antisecretory medication compared to non-users (82, 83). Data from a Barrett's esophagus surveillance program showed a lower incidence of dysplasia among patients on a PPI compared to those without prior PPI therapy, suggesting a potential preventive effect for esophageal cancer (84). Although retrospective, a second report which assessed the number of esophageal and gastric cancers diagnosed subsequent to negative findings on an initial EGD found a significantly greater number of delayed diagnosis for gastric adenocarcinoma among PPI-users (versus non-users); however, there was no difference for esophageal adenocarcinoma between groups (85). There is no evidence demonstrating that PPI use prior to EGD would preclude the diagnosis of esophageal cancer in patients presenting with dysphagia.

No study has directly compared the safety and efficacy of an empiric PPI trial first (with EGD for those who do not respond completely) to prompt EGD for all patients (with optional PPI treatment while waiting for the EGD). However, any delay in diagnosis as a result of an empiric PPI trial, as recommended in the statement, would only be four weeks, which would be unlikely to impact cancer outcome. Canadian consensus guidelines on wait times recommend that patients with severe or rapidly progressive dysphagia, or a high likelihood of cancer, be assessed within two weeks (58). However, for patients with stable dysphagia without other alarm features, the wait time for an outpatient EGD from the time of consultation is generally

longer than four weeks (86). Therefore, the consensus group recommended empiric PPI therapy and suggested scheduling an EGD, which can be cancelled if symptoms completely resolve to avoid unnecessary investigations.

Section 5: Role of Endoscopy in the Evaluation of Esophageal Dysphagia

Statement 5.1: In patients with persistent esophageal dysphagia, we recommend endoscopy as the initial test to maximize diagnostic yield.

- GRADE: Strong recommendation, very low-quality evidence. Vote: agree strongly, 78%; agree with minor reservation, 22%
Studies comparing the diagnostic accuracy of EGD and barium esophagram were discussed in statement 3.1 (59–64). Results of these studies are conflicting, with some reporting greater accuracy with barium esophagram (59, 63) and others with EGD (60–62, 64). EoE, which is also an increasingly common finding in patients with dysphagia (5, 87, 88), requires EGD with biopsy to establish a diagnosis. Abnormal findings (such as retained food in a dilated esophagus) on EGD may suggest achalasia, which can then be further defined with manometry or barium esophagram (69, 89).

The consensus group concluded that when investigations are considered in patients with persistent dysphagia, EGD should be the initial test, to evaluate inflammatory or structural mucosal lesions.

Statement 5.2: In all patients undergoing endoscopy for esophageal dysphagia, unless there are clear features of erosive reflux esophagitis, we recommend esophageal biopsy be performed to detect mucosal pathology.

- GRADE: Strong recommendation, low-quality evidence. Vote: agree strongly, 78%; agree with minor reservation, 11%; agree with major reservation, 11%.
EoE, generally defined as ≥ 15 (5, 90, 91) or ≥ 20 (92–94) eosinophils per high-powered field, requires EGD with biopsy to make a diagnosis. The prevalence of EoE is about 8–9% among patients with dysphagia (5, 87), compared to about 3.1% in unselected patients (92). Conversely, about 55–73% of patients with EoE have dysphagia (49, 92, 93, 95, 96). The prevalence of EoE has been increasing (5), which cannot entirely be explained by better recognition (97, 98).

Patients with EoE can present with a normal appearing mucosa on EGD (47, 49, 94); therefore, mucosal biopsy is recommended for the assessment of dysphagia. A longitudinal study has showed that education on the need for biopsy can increase detection of EoE by 40% (88). In patients with dysphagia, biopsy is also needed to detect relatively rare conditions such as lymphocytic esophagitis (95), esophageal tuberculosis (99), linitis plastica adenocarcinoma (100), and esophageal lichen planus (101).

Guidelines for the management of EoE, from the American Gastroenterological Association (AGA) (90) and the American

College of Gastroenterology (ACG) (102), as well as the recent European guidelines (103), recommend two to four esophageal biopsies from at least two locations (i.e., proximal and distal esophagus) from all patients in whom EoE is being considered, regardless of the gross appearance of the mucosa. When the number of biopsies reaches six to nine, diagnostic sensitivity approaches 100% (104–106).

The consensus group agreed with previous recommendation on the assessment of EoE and recommended multiple biopsies at multiple sites in patients in whom EoE is suspected, even if the mucosa appears to be normal endoscopically.

In patients with typical erosive esophagitis (Los Angeles Classification, Grade B or higher), biopsy findings may be inadequate to confirm the diagnosis of EoE since eosinophils are also found in erosive esophagitis, and dysphagia is frequent in patients with erosive esophagitis. In those patients, the committee suggests to first treat the patient with PPI for at least eight weeks. If dysphagia does not resolve, consider repeat endoscopy with biopsy to assess for the presence of EoE, and in those with severe erosive esophagitis, repeat endoscopy to evaluate for the presence of Barrett's esophagus.

Section 6: Role of Esophageal Manometry in the Evaluation of Esophageal Dysphagia

Statement 6.1: Esophageal manometry is the gold standard for diagnosing esophageal motility disorders.

- GRADE: Strong recommendation, very low-quality evidence. Vote: agree strongly, 89%; agree with minor reservation, 11%
Statement 6.2: In patients with persistent esophageal dysphagia, after structural and inflammatory causes have been ruled out, we recommend esophageal manometry to evaluate esophageal motility disorders.
- GRADE: Strong recommendation, very low-quality evidence. Vote: agree strongly, 100%

In clinical practice, EGD is generally the first diagnostic test to evaluate structural and inflammatory disorders, followed by manometry when motility disorders are the suspected cause of dysphagia. In patients with dysphagia and a normal EGD assessment, subsequent esophageal manometry had a higher diagnostic yield than barium esophagram (4.6% versus 33.3%) (4). As described in statement 3.3, there is good concordance between manometry and barium esophagram in patients with dysphagia (72, 73), although some studies show good specificity but poor sensitivity of barium esophagram in patients with dysphagia and abnormal manometry studies (70, 71, 74–76).

Manometry has demonstrated clinical utility when used in patients with dysphagia after prior non-diagnostic EGD and/or barium esophagram (8, 9). In a survey of patients who had dysphagia as an indication for manometry, new information was obtained in 90% of patients; the diagnosis

was changed in 51% (most common new diagnoses were achalasia, IEM and EGJ outflow obstruction), and management was changed in 69% (8). Similarly, in another observational study, 79.4% of patients with dysphagia had abnormal results on manometry, with the most frequent diagnosis being achalasia (53.7%) (9).

The consensus group concluded that manometry should be performed in patients who continue to have dysphagia once structural and inflammatory (including GERD and EoE) causes have been ruled out by a normal EGD with appropriate biopsies.

Statement 6.3: In patients with dysphagia, we suggest high-resolution esophageal manometry over conventional esophageal manometry to improve diagnostic performance.

- **GRADE:** Strong recommendation, very low-quality evidence. Vote: agree strongly, 56%; agree with minor reservation, 33%; agree with major reservation, 11%

High resolution esophageal manometry (HREM) has theoretical technologic advantages over conventional manometry in the diagnosis of esophageal motility disorders. Low-quality data suggest HREM can provide more manometric information than conventional manometry and may increase diagnostic yield in patients with dysphagia (107–109) and unselected patients (110, 111). Use of the Chicago Classification with HREM may increase diagnostic accuracy (107, 110) and enhance consistency in reporting.

The consensus group concluded that HREM is preferred, when available. The group also recommended that recordings be interpreted by trained and experienced clinicians and that it is inadequate to rely solely on computer interpretation to ensure diagnostic accuracy.

CONCLUSIONS

The suggested diagnostic approach to uninvestigated dysphagia is summarized in figure 1. Oropharyngeal dysphagia should be considered first and ruled out in all patients presenting with uninvestigated dysphagia. If oropharyngeal dysphagia is suspected, referral to a speech language pathologist, or other appropriate specialist, for further investigation and management is recommended. Patients with symptoms of esophageal dysphagia should be assessed by history for alarm features that require urgent investigations (e.g., endoscopy or other imaging studies, such as computed tomography or ultrasound). A PPI trial can be considered in patients who are < 50 years old and have no other alarm features. If dysphagia persists after a four-week PPI trial, investigations to assess inflammatory or structural lesions are recommended. Once inflammatory or structural lesions have been ruled out by endoscopy (with biopsy as indicated) and/or barium esophagram, esophageal manometry should be used to evaluate all patients with persistent dysphagia. In a patient with subjective sensation of dysphagia, when thorough investigations have excluded oropharyngeal and esophageal causes, a diagnosis of functional dysphagia should be considered (112).

Future Directions

In the first iteration of the statements, the committee intended to recommend using symptoms to differentiate oropharyngeal from esophageal dysphagia. In clinical practice, many clinicians have found that “the timing of dysphagia (i.e., immediate vs delayed after the initiation of swallow is completed)” is often helpful in distinguishing between oropharyngeal dysphagia and esophageal dysphagia. After an extensive literature

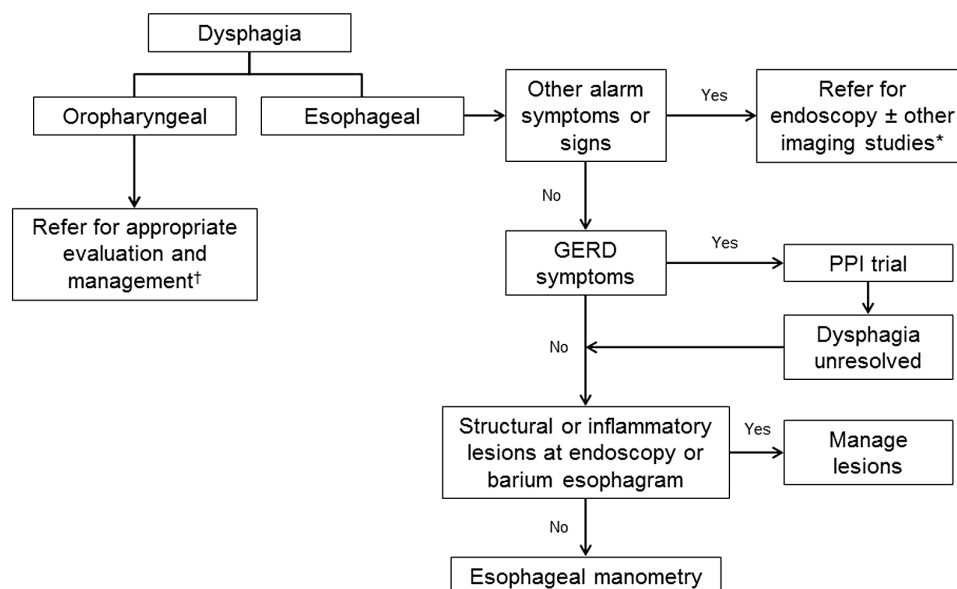


Figure 1. Suggested diagnostic approach to uninvestigated dysphagia. *Imaging studies could include computed tomography (CT) and ultrasound. †Expertise (e.g., speech language pathologist or occupational therapist) and assessments (e.g., videofluoroscopic swallowing study [VFSS] or fiberoptic endoscopic evaluation of swallowing [FEES]) vary depending on regional availability.

search, we were unable to identify any direct evidence demonstrating that symptoms subjectively reported by patients can help distinguish oropharyngeal from esophageal dysphagia. The lack of data on the sensitivity and specificity of patient-reported symptoms in differentiating the types of dysphagia was identified as a knowledge gap, despite the fact that this is an important first step in the clinical assessment of patients presenting with dysphagia and affects management decisions. Furthermore, because GERD is common in the general population and is frequently associated with dysphagia, there is a need for well-conducted RCTs on the impact of empiric PPI therapy in patients < 50 years old with dysphagia and without other alarm symptoms compared to early EGD. Further studies to assess the diagnostic accuracy of HREM over conventional manometry in the evaluation of patients with different esophageal motility disorders are warranted to determine optimal utilization.

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Canadian Association of Gastroenterology Statement

This clinical practice guideline (CPG) for the assessment of uninvestigated esophageal dysphagia was developed under the direction of Dr. Louis Liu, in accordance with the policies and procedures of the Canadian Association of Gastroenterology (CAG) and under the direction of CAG Clinical Affairs. It has been reviewed by the CAG Practice Affairs and Clinical Affairs Committees and the CAG Board of Directors. The CPG was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of experts on this topic. The CPG aims to provide a reasonable and practical approach to care for specialists and allied health professionals charged with the duty of providing optimal care to patients and families; however, the CPG can be subject to change as scientific

knowledge and technology advance and as practice patterns evolve. The CPG is not intended to substitute for physicians' use of their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available, and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

CONFLICT OF INTEREST

The authors do not have any industry or government relationships to report (AL, ND, NJ, RM, WP, GL).

Author Contributions

All members of the consensus group (with the exception of GL and FT) reviewed the literature, drafted the statements, and voted on the recommendations. GL and FT assessed the evidence and provided GRADE evaluations. The chair drafted the initial manuscript, which was reviewed, revised, and approved by all members of the consensus group. Subsequently it was made available to all CAG members for comments prior to submission for publication.

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APPENDIX**Online Appendix 1. Search strategies used for EMBASE and MEDLINE and CENTRAL**

(All searches were updated to March 2015)

Statement 1

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <September 2012>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1974 to 2012 October 04>

Search Strategy:

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1  exp Deglutition Disorders/ (74138)
2  exp Deglutition/ (18795)
3  dysphagia.mp. (55554)
4  exp dysphagia/ (74138)
5  exp swallowing/ (18795)
6  swallow*.mp. (46835)
7  1 or 2 or 3 or 4 or 5 or 6 (122463)
8  (esophag* or oesophag*).mp. (346880)
9  oropharyn*.mp. (36252)
10 8 and 9 (3428)
11 7 and 10 (1178)
12 (oral-pharyn* or oropharyn*).mp. (37124)
13 (eso-phag* or oeso-phag* or esophag* or oesophag*).mp. (346882)
14 12 and 13 (3696)
15 7 and 14 (1306)
16 15 not 11 (128)
17 (eso-phag* or oeso-phag* or esophag* or oesophag* or oral-pharyn* or oropharyn*).ti. (179875)
18 (dysphagia or swallowing disorder* or deglutition).ti. (11353)
19 17 and 18 (1911)
20 19 not 11 (1767)
21 16 or 20 (1883)
22 limit 21 to english language [Limit not valid in CCTR,CDSR; records were retained] (1491)
23 remove duplicates from 22 (864)
24 (animals not (humans and animals)).sh. (3699389)
25 (animal not (humans and animal)).sh. (1804242)
26 24 or 25 (5503631)
27 23 not 26 (860)
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Statement 2

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <September 2012>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1974 to 2012 October 08>

Search Strategy:

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1  Deglutition Disorders/ (47102)
2  Deglutition/ (18798)
3  Esophageal Motility Disorders/ (2370)
4  dysphagia/ (47102)
5  swallowing/ (18798)
6  1 or 2 or 3 or 4 or 5 (62704)
7  exp Medical History Taking/ (185694)
8  exp Physical Examination/ (1119282)
9  exp anamnesis/ (167864)
10 7 or 8 or 9 (1269979)
11 6 and 10 (3562)
12 ((clinical manifestation* or alarm symptom*) adj10 (dysphagia or deglutition or swallowing)).mp. (210)
13 (((patient* adj2 history) or (history adj2 tak*) or (medical history or medical record*)) adj10 (dysphagia or deglutition or swallowing)).mp. (1065)
14 ((historical or physical examination* or anamnesis) adj10 (dysphagia or deglutition or swallowing)).mp. (2024)
15 12 or 13 or 14 (3201)
16 11 or 15 (4759)
17 (diagnos* and (dysphagia or deglutition or swallowing)).ti. (566)
18 16 or 17 (5265)
19 limit 18 to english language [Limit not valid in CCTR,CDSR; records were retained] (4481)
20 remove duplicates from 19 (4051)
21 (animals not (humans and animals)).sh. (3699389)
22 (animal not (humans and animal)).sh. (1804559)
23 21 or 22 (5503948)
24 20 not 23 (3925)
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Statement 3

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1974 to 2012 September 11>

Search Strategy:

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1  *Deglutition Disorders/ (18054)
2  *Deglutition/ (6754)
3  *swallowing/ (6754)
4  swallowing disorder*.ti,ab. (1709)
5  *dysphagia/ (18054)
6  dysphagia.ti,ab. (36959)
7  1 or 2 or 3 or 4 or 5 or 6 (49114)
8  Barium.ti,ab. (37465)
9  Barium meal/ (2373)
10 Barium Sulfate/ (14265)
11 *Barium/ (5809)

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- 12 *Contrast Media/ (47468)
 13 contrast media.ti,ab. (20452)
 14 *esophagography/ or esophagram.ti,ab. or oesophagram.ti,ab. (2530)
 15 8 or 9 or 10 or 11 or 12 or 13 or 14 (107252)
 16 7 and 15 (3503)
 17 remove duplicates from 16 (2289)
 18 limit 17 to english language (1954)
 19 limit 18 to humans (1655)

Statement 4

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1974 to 2012 September 20>

Search Strategy:

-
- 1 Deglutition Disorders/ (46523)
 2 Deglutition/ (18527)
 3 dysphagia.mp. (54386)
 4 dysphagia/ (46523)
 5 (swallow\$ adj2 disorder*).mp. (2026)
 6 1 or 2 or 3 or 4 or 5 (74759)
 7 exp Gastroesophageal Reflux/ (60269)
 8 exp esophagitis/ (30787)
 9 (esophagitis or oesophagitis).mp. (39022)
 10 ((gastro adj2 oesophageal adj2 reflux) or (gastro adj2 esophageal adj2 reflux)).tw. (10052)
 11 (((gastro-esophageal adj2 reflux) or gastro-oesophageal adj2 reflux).tw. (10040)
 12 (gastro?esophageal adj2 reflux).tw. (29377)
 13 *duodenogastric reflux/ (1827)
 14 (duodenogastric adj2 reflux).tw. (1860)
 15 (acid adj3 reflux).tw. (5366)
 16 (GORD or GERD).mp. (13798)
 17 (NERD or NORD or EoE).mp. (6344)
 18 Esophagitis, Peptic/ (13244)
 19 Eosinophilic Esophagitis/ (1681)
 20 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 18 or 19 (91647)
 21 6 and 20 (10318)
 22 exp proton pump inhibitors/ (46911)
 23 (proton adj2 pump adj2 inhibitor\$.mp. (31325)
 24 exp omeprazole/ (32296)
 25 omeprazole.tw. (15190)
 26 (lansoprazole or lanzoprazole).tw. (4340)
 27 esomeprazole.mp. (5070)
 28 pantoprazole.mp. (6707)
 29 rabeprazole.mp. (4119)
 30 tenatoprazole.mp. (69)
 31 (Dexlansoprazole or Kapidex or Dexilant).mp. (139)
 32 (PPI or PPIs).mp. (19354)

- 33 proton pumps/ (7948)
 34 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (78730)
 35 21 and 34 (1702)
 36 remove duplicates from 35 (1379)
 37 limit 36 to english language (1241)

Statement 5

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <September 2012>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1974 to 2012 October 05>

Search Strategy:

-
- 1 *Deglutition Disorders/ (18143)
 2 *Deglutition/ (6790)
 3 swallowing disorder*.ti,ab. (1749)
 4 *dysphagia/ (18143)
 5 dysphagia.ti,ab. (37970)
 6 1 or 2 or 3 or 4 or 5 (50193)
 7 *Endoscopy/ or *Endoscopy, Gastrointestinal/ or *Endoscopy, Digestive System/ (60272)
 8 Endoscopy, Digestive System/mt (1357)
 9 Endoscopy, Digestive System/ut (48)
 10 Endosonography/mt (2111)
 11 Endosonography/ut (50)
 12 *Endosonography/ (11771)
 13 Esophagoscopy/mt (1766)
 14 Esophagoscopy/ut (30)
 15 *esophagoscopy/ (7051)
 16 Endoscopy, Gastrointestinal/mt (3685)
 17 Endoscopy, Gastrointestinal/ut (144)
 18 *fiberscope endoscopy/ or *high resolution endoscopy/ or *digestive tract endoscopy/ or *gastrointestinal endoscopy/ (14205)
 19 *endoscopic echography/ (6975)
 20 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (80254)
 21 6 and 20 (1539)
 22 ((endoscopic or endoscopy or endoscope or scope or EGD or endosonograph* or esophagoscop* or oesophagoscop*) adj10 (dysphagia or swallowing disorder* or deglutition)).ti,ab. (2524)
 23 21 or 22 (3668)
 24 *Biopsy, Fine-Needle/ or *Biopsy/ or *Biopsy, Needle/ (48053)
 25 Biopsy/mt, ut (9135)
 26 Biopsy, Fine-Needle/mt, ut (1785)
 27 Biopsy, Needle/mt, ut (8101)

- 28 *biopsy technique/ (408)
- 29 *oral biopsy/ or *biopsy technique/ or *duodenum biopsy/ or *esophagus biopsy/ or *gastrointestinal biopsy/ or *endoscopic biopsy/ (1698)
- 30 24 or 25 or 26 or 27 or 28 or 29 (57579)
- 31 6 and 30 (68)
- 32 ((biopsy or biopsies) adj10 (dysphagia or swallowing disorder* or deglutition)).ti,ab. (301)
- 33 31 or 32 (359)
- 34 23 or 33 (3892)
- 35 limit 34 to english language [Limit not valid in CCTR,CDSR; records were retained] (3053)
- 36 (animals not (humans and animals)).sh. (3699389)
- 37 (animal not (humans and animal)).sh. (1804242)
- 38 36 or 37 (5503631)
- 39 35 not 38 (3032)
- 40 remove duplicates from 39 (1955)

Statement 6

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <September 2012>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1974 to 2012 October 08>

Search Strategy:

- 1 *Deglutition Disorders/ (18150)
- 2 *Deglutition/ (6790)
- 3 *Esophageal Motility Disorders/ (1509)
- 4 dysphagia/ (47102)
- 5 swallowing disorder*.tw. (1754)
- 6 dysphagia.tw. (38058)
- 7 1 or 2 or 3 or 4 or 5 or 6 (68249)
- 8 *Manometry/ (8575)
- 9 exp esophagus manometry/ (2303)
- 10 manometry.tw. (18073)
- 11 8 or 9 or 10 (25112)
- 12 7 and 11 (3966)
- 13 remove duplicates from 12 (2569)
- 14 limit 13 to english language [Limit not valid in CCTR,CDSR; records were retained] (2155)
- 15 (animals not (humans and animals)).sh. (3699389)
- 16 (animal not (humans and animal)).sh. (1804559)
- 17 15 or 16 (5503948)
- 18 14 not 17 (2145)
