Dysphagia: Thinking outside the box

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Abstract
Dysphagia is a common symptom that is important to recognise and appropriately manage, given that causes include life threatening oesophageal neoplasia, oropharyngeal dysfunction, the risk of aspiration, as well as chronic disabling gastroesophageal reflux (GORD). The predominant causes of dysphagia varies between cohorts depending on the interplay between genetic predisposition and environmental risk factors, and is changing with time. Currently in white Caucasian societies adopting a western lifestyle, obesity is common and thus associated gastroesophageal reflux disease is increasingly diagnosed. Similarly, food allergies are increasing in the west, and eosinophilic oesophagitis is increasingly found as a cause. Other regions where cigarette smoking is still prevalent, or where access to medical care and antisecretory agents such as proton pump inhibitors are less available, benign oesophageal peptic strictures, Barrett’s oesophagus, adeno- as well as squamous cell carcinoma are endemic. The evaluation should consider the severity of symptoms, as well as the pre-test probability of a given condition. In young white Caucasian males who are atopic or describe heartburn, eosinophilic esophagitis and gastroesophageal reflux disease will predominate and a proton pump inhibitor could be commenced prior to further investigation. Upper gastrointestinal endoscopy remains a valid first line investigation for patients with suspected oesophageal dysphagia. Barium swallow is particularly useful for oropharyngeal dysphagia, and oesophageal manometry mandatory to diagnose motility disorders.

Key words: Dysphagia; Oesophagus; Eosinophilic; Manometry; Gastroesophageal reflux; Aspiration; Food bolus impaction

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Core tip: Dysphagia may represent serious and life-threatening pathology such as oesophageal neoplasia or oropharyngeal dysfunction capable of causing aspiration. In young white Caucasian males, eosinophilic esophagitis and gastroesophageal reflux disease will predominate and a proton pump inhibitor could be commenced prior to further investigation.
INTRODUCTION

Dysphagia is a common symptom in patients presenting to both generalist and specialist medical practitioners[1,2]. The key initial consideration for clinicians is to rule out life-threatening pathology such as neoplasia, and to identify patients who are at risk of aspiration such that immediate intervention can occur[3]. Dysphagia is most commonly due to chronic benign disorders, although it can be associated with appreciable morbidity and impaired quality of life (QOL)[4]. Gastroesophageal reflux disease (GORD) is the major cause in younger individuals, whilst oropharyngeal dysphagia (OD) secondary to cerebrovascular disease is more frequent in the elderly[3,4]. Dysphagia as a symptom attributable to GORD in younger adults does not automatically mandate investigation, rather a trial of a proton pump inhibitor (PPI) and strict follow-up to ensure symptomatic resolution might be sufficient[5]. OD and oesophageal dysphagia can often be reliably differentiated symptomatically and might help reduce the risk of aspiration in OD[6]. A comprehensive awareness of the multitude of potential causes of dysphagia, including common medications and rheumatological conditions, is necessary to allow for efficient and thorough evaluation. Judicious investigation with the appropriate choice of tests in order to consider both common and unusual aetiologies is required; high quality endoscopy with care to take sufficient oesophageal biopsies even if mucosa looks normal (e.g., eosinophilic oesophagitis (EoE)), high resolution oesophageal manometry (HRM) in suspected motility disturbance, barium swallow and where appropriate, cross-sectional imaging [e.g., computed tomography (CT) scan]. The escalating frequency of GORD and EoE, and the increase in mean age (and associated conditions such as CVA) will ensure that dysphagia remains a common presentation in the future[10]. This review attempts to present a contemporary understanding and approach to patients with dysphagia.

AETIOLOGY AND PATHOGENESIS

Dysphagia is the subjective awareness of impairment in the passage of food from the oropharynx to the stomach, and therefore may signify an actual delay in bolus transit, or merely the sensation thereof[12]. It is useful to consider the anatomical structures implicated in swallowing (including innervation), and the location of pathology within (Figure 1)[10]. The process of swallowing, whereby food or liquid travels from the mouth to the stomach, involves a complex sequence of muscular contraction and relaxation, involving striated (oropharynx and upper 1/3rd of the oesophagus) and smooth muscle (lower 2/3rd of the oesophagus) that is controlled by motor neurons of the brainstem, and autonomic innervation (of the myenteric plexus) respectively[10,11]. The oropharyngeal component is

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Dysphagia is the subjective awareness of impairment in swallowing of saliva, liquid or solid food. The prevalence varies by age of cohort, method of data collection, and if the dysphagia is classified as acute or chronic[1,4,9]. A community survey of 1000 individuals in Sydney Australia, demonstrated a prevalence of dysphagia of 16% (defined as ever having the symptom), although few (1%) reported dysphagia as chronic or severe[4]. GORD, hypertension and psychological symptoms (anxiety and depression) were independently associated with dysphagia[4]. Subjectivity in symptom reporting and the contribution of GORD have emerged as important themes in contemporary studies of dysphagia[1]. A study of patients with GORD reported resolution of dysphagia with PPI[10]. General practice cohorts have found a frequency of dysphagia of up to 23%, thus reflecting the significant health care burden taken up by this patient group[1]. Self-reported dysphagia is often variably defined[11], an isolated globus sensation can erroneously be considered a form of dysphagia.

In a large survey of an adult United States population (n = 7640, 3669 respondents), 17% of respondents reported “infrequent” (<1 episode per week) and 3% “frequent” (>1 episode per week) dysphagia[11]. On interrogation of these respondents’ medical files, symptoms of heartburn and endoscopic diagnosis of GORD were significantly associated with both the “frequent” and “infrequent” cohorts[1]. Perhaps due to the limited sample size and old age of the respondents (mean 62 years), other typical conditions were not statistically associated with dysphagia. Primary oesophageal conditions (EoE, achalasia, cancer) and systemic conditions (scleroderma, rheumatoid arthriti) were only reported amongst the “frequent” dysphagia group[1]. Therefore, clinically significant (or frequent) dysphagia should alert the clinician to serious underlying pathology, whilst infrequent dysphagia is most likely to represent GORD and a trial of acid suppression may be worthwhile in the first instance provided there are no alarm symptoms. This view is supported by several experts in the field (see below).
those with chronic severe GORD and there is some evidence that both may independently influence oesophageal peristalsis\(^\text{[17,18]}\). Treatment of Barrett’s oesophagus with endoscopic mucosal resection (EMR) and radiofrequency ablation can lead to fibrosis\(^\text{[19]}\). The Schatzki ring (a mucosal ring of the distal oesophagus), occurs just proximal to the gastroesophageal sphincter, often within a hiatus hernia, and is relatively common\(^\text{[20,21]}\). Barium swallow reveals Schatzki ring in 5%-15% of patients with HH\(^\text{[8]}\). The association with dysphagia and its cause (congenital, secondary to GERD or even EoE) are debated\(^\text{[22]}\). Proximal oesophageal webs have been described in individuals with dysphagia. An association with iron deficiency anaemia (the Plummer-Vinson syndrome) was apparently common in the first half of last century, although is rarely reported today\(^\text{[23,24]}\). EoE is perhaps the most important, benign cause of dysphagia behind GORD. It is increasingly common and may be responsible for some cases previously diagnosed as fibrous strictures or webs\(^\text{[7]}\). This is an important consideration amongst Caucasian patients in western countries, and is readily treatable (see below)\(^\text{[8,25]}\). The prevalence of EoE is estimated at between 1 in 500 and 1 in 1000 adult Caucasian males\(^\text{[26]}\). The importance of EoE is redoubled by the frequent occurrence of food bolus obstruction, a complication that is associated with significant morbidity including the need for hospitalisation, upper gastrointestinal endoscopy (UGE) and (rarely but catastrophically) oesophageal perforation\(^\text{[27]}\).

Non-obstructive gastro-oesophageal reflux disease

Many patients that describe dysphagia will have normal investigations including UGE and high-resolution manometry (HRM), suggesting that a dysfunction of the somatosensory as opposed to neuromuscular apparatus might be present\(^\text{[26,29]}\). A unifying hypothesis to explain this apparent dichotomy is that a minor disturbance in peristalsis (caused for example by GORD, or non-erosive reflux disease - NERD) may be below the threshold of detection even by sensitive HRM, yet be experienced by the patient as dysphagia. Indeed, many people will describe a resolution of symptoms with proton pump inhibition (PPI). Interventions aimed at modulating the somatosensory system have hence been advocated\(^\text{[26,29]}\).

Primary motility disturbance

Achalasia is the prototypical condition classified as a primary (isolated to the oesophagus) disorder of oesophageal motility, yet is quite rare, with an estimated prevalence of 0.17% in individuals undergoing endoscopy\(^\text{[30]}\). Patients typically present with a chronic history of dysphagia for liquids and/or solids, and often with retrosternal discomfort, heartburn and weight loss\(^\text{[31]}\). The underlying pathophysiology is of an imbalance between excitatory

Initially voluntary (including chewing). This is followed by an involuntary phase initiated by food entering the pharynx, whereby the swallowing reflex causes simultaneous relaxation and contraction of the soft palate, upper oesophageal sphincter, oesophagus and lower oesophageal sphincter\(^\text{[6]}\).

Causes of dysphagia vary across the world, and there is evidence of a change in the relative proportion of the various disease states in the last few decades\(^\text{[8]}\). In the United States, benign oesophageal stricture has become less common, whilst EoE is increasing, along with oesophageal adenocarcinoma\(^\text{[8]}\). This pattern is mirrored in other Western nations\(^\text{[18]}\). Oesophageal squamous cell cancer remains a common condition in Asia, whilst Chagas disease still is prevalent in some regions of South America\(^\text{[18]}\).

The oesophageal lumen can become narrowed by inflammation (e.g., erosive reflux disease or EoE), neoplasia or fibrous stricture, or can be compressed externally by lymph nodes or degenerative disease of the cervical spine\(^\text{[8,12-15]}\).

Luminal stenosis

Narrowing of the oesophageal lumen by inflammation, stricture, web or tumour can result in dysphagia\(^\text{[16]}\). Distal oesophageal inflammation from GORD can result in dysphagia due to transient decrement in peristaltic vigour, and if sustained can lead to fibrous stricture formation\(^\text{[8,15]}\). Barrett’s oesophagus and/or sliding hiatus hernia (HH) are present in > 80% of
and inhibitory neurons of the myenteric plexus at the distal oesophageal sphincter, with a decrement in inhibitory innervation (nitrous oxide, or vasoactive intestinal peptide) leading to aperistalsis and failure of relaxation of the lower oesophageal sphincter during primary swallowing in classical (Type I) achalasia, pan-oesophageal pressurisation in early (Type II) achalasia or spasm of the oesophageal body (Type III achalasia), but manometry is required to accurately define subtype[32]. Current literature suggests that achalasia is an autoimmune condition associated with antibodies directed at the myenteric plexus and linked to HLA class II DR and DQ alleles[33]. Distal oesophageal spasm and “jackhammer” oesophagus (formerly, nutcracker oesophagus) are disorders of distal oesophageal hypercontractility which can present as dysphagia and/or chest pain and are defined with high resolution manometry as per the recent Chicago classification update (see below)[34-37]. These primary, major disorders of oesophageal motility, may be part of a disease spectrum with shared pathogenesis[38-40]. It is important to always consider secondary achalasia (pseudo-achalasia) that can result from neoplastic infiltration of the distal oesophagus, or be secondary to infection (Chagas disease, primarily occurring in South America)[41,42].

The advent of HRM and subsequent diagnostic algorithms has led to a reconsideration of minor disorders of peristalsis as a cause of dysphagia (defined by the Chicago Classification)[38]. Many patients presenting with dysphagia will have ineffective oesophageal motility in the distal oesophagus or fragmented peristalsis (defined by HRM and the Chicago Classification)[39]. Previously, it had been demonstrated that these abnormalities are frequently found in patients with GORD[40]. The symptom of dysphagia did not correlate with minor disorders or peristalsis on HRM[28,44]. An evolving consensus is arguably emerging that these “abnormalities” may lack clinical application and relevance[44].

**Rheumatological conditions**

To ensure a systematic evaluation occurs and that relevant pathology is not overlooked, an awareness of rheumatological and neurological conditions, medications that may cause oesophageal dysmotility, and causes of extrinsic anatomical compression is required[34,45-48]. Dysphagia is frequently reported by patients with Sjögren’s syndrome, systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD) and rheumatoid arthritis, not to mention the more commonly recognised association with systemic sclerosis (as part of the CREST syndrome)[49] (Table 1). More than 1/3 of patients with Sjögren’s syndrome report dysphagia, caused both by xerostomia and thus deficient lubrication of the food bolus, and by abnormal peristalsis demonstrable by oesophageal manometry (particularly in the upper 1/3 of the oesophagus)[45,49].

Similarly, patients with SLE and MCTD frequently describe dysphagia, and proximal oesophageal peristalsis is often weak or fragmented[45]. The cause of the abnormal motility in these conditions is unknown, although an inflammatory myopathy or neuropathy has been postulated[45]. Manometry was unable to correlate these symptoms with dysmotility[45]. In patients with rheumatoid arthritis, distal oesophageal peristalsis can be weak or fragmented; although life-threatening subluxation of the cervical spine needs to be considered[40]. Oesophageal dysmotility as a feature of the CREST syndrome is the best known and most studied of the rheumatological conditions, although dysphagia is often overshadowed by heartburn[51,52]. The pathophysiological process of fibrous replacement of the smooth muscle of the mid and lower oesophagus leads to incompetence of the lower oesophageal sphincter (LOS) and the clinical sequelae of GORD and dysphagia[53].

Extrinsic compression of the oesophagus can be a feature of osteoarthritis of the cervical spine, with (particularly) anterior osteophyte formation[13]. This is also occurs in a more florid fashion with diffuse idiopathic skeletal hyperostosis (DISH)[54]. Ironically, neurosurgical interventions for degenerative cervical spine disease (such as anterior discectomy) can result in dysphagia both in the short term (with post-operative swelling, or rarely because of damage to the cranial nerves) or long term (compression secondary to a cage implant, if placed)[48]. Other causes of extrinsic compression include mediastinal or hilar lymphadenopathy (e.g. due to haematological or disseminated solid organ neoplasia) and goitre[14,55].

**Medications**

Medications cause or contribute to dysphagia by influencing oesophageal peristalsis, xerostomia, as a secondary consequence of esophagitis (“pill oesophagitis”), or by causing GORD (Table

| Medication | Putative mechanism |
|------------|--------------------|
| Antipsychotic, e.g., olanzapine[45], clozapine[42] | Block dopamine receptors |
| Tricyclic antidepressant, e.g., amitriptyline[46] | Anticholinergic, decreased saliva and impairment secondary peristalsis |
| Opioids[34] | Increase lower oesophageal contractility, oesophageal spasm |
| Iron supplements | Localised oesophagitis[29,40] |
| Potassium supplements | Smooth muscle relaxation (including lower oesophageal sphincter) |
| NSAIDs | |
| Tetracyclines | |
| Macrolides | |
| bisphosphonates | |
| Calcium channel blockers | |
| Alcohol | |
| Theophylline | |

**Table 1 Medications implicated in causing dysphagia**
Sedative agents can lead to compromise of airway maintenance and thus aspiration is a risk. Finally, medications that have a local or systemic immunosuppressant effect can predispose to infective oesophagitis. Among individuals with a psychiatric diagnosis, dysphagia may relate, at least in part, to the use of psychotropic medication. The anticholinergic and antidopaminergic effects of antipsychotics and tricyclic antidepressants have been implicated, not only in causing a dry mouth (anticholinergic) thus limiting lubrication of the food bolus, but also in decreasing the coordination and strength of peristalsis and the timing of lower oesophageal sphincter relaxation. It is also possible that serotonergic pathways may be responsible for the dysphagia caused by clozapine, although this hypothesis is perhaps refuted by the absence of case reports relating SSRIs to dysphagia.

Individuals with psychiatric diagnoses may also have an increased rate of neurological disorders (such as Parkinson’s disease), particularly among older individuals in residential care, that can cause dysphagia. The use of opiates, even if low dose and over the counter, can lead to hypercontractile or hypertensive sequelae of the oesophagus and/or LOS, sometimes even mimicking Type III achalasia.

### Neurogenic dysphagia - Common causes

| Condition                  | Description                                      |
|----------------------------|--------------------------------------------------|
| Parkinson’s disease         | Oropharyngeal and oesophageal dysphagia is possible |
| Multiple sclerosis          | Oropharyngeal and oesophageal dysphagia is possible |
| Cerebrovascular disease     | Oropharyngeal dysphagia typical                  |
| Motor neuron disease        | Features of bulbar and pseudobulbar palsy possible |
| Myasthenia gravis           |                                                  |
| Myopathy (various, including inflammatory) | Oropharyngeal and proximal oesophage              |
| Cerebellar pathology (various) |                                               |

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Awareness of Parkinson’s disease as a cause of dysphagia is of importance to gastroenterologists given the recent finding of neurological pathology beyond the brainstem. Furthermore other gastrointestinal symptoms such as constipation may precede the characteristic clinical syndrome of tremor, rigidity and bradykinesia. Other neurogenic causes of dysphagia are outlined in Table 3.

**CLINICAL ASSESSMENT**

The aetiology of dysphagia can be variably classified, but traditionally oropharyngeal dysphagia (OD) and oesophageal dysphagia are defined as distinct groups because the immediate treatment approach to the former is to consider aspiration risk and dietary modification (Figure 2). It has been estimated that the presence of one or more of a 4-symptom cluster can predict OD accurately: delay in oropharyngeal initiation of swallowing, deglutitive cough, deglutitive nasal aspiration and the need to repetitively swallow to clear nasal secretions. OD is principally managed by neurologists, ENT surgeons and speech pathologists, and is therefore beyond the focus of this review. Further useful sub-classifications of oesophageal disease include dysphagia to solids only (implying an anatomical distortion) or to liquids and solids (implying a physiological or motility disturbance), although the precision of any such clinical “rule of thumb” is not absolute. Longstanding symptoms of mixed dysphagia would normally suggest a motility disturbance.

**INVESTIGATIONS**

UGE remains a central tool in the investigational algorithm, being essential for the diagnosis of oesophageal malignancy, refractory GORD and EoE. At least middle and lower biopsies of the oesophagus should be taken in patients with dysphagia, even when the macroscopic appearance is normal, primarily with the intention of excluding EoE. The role of UGE as a mandatory primary investigation is debated. Whilst dysphagia can signify life-threatening pathology such as oesophageal or gastric neoplasia, in the majority UGE will be normal or demonstrates only mild erosive disease, leading several experts to advocate a trial of PPI first in otherwise healthy subjects.

This is a departure from orthodox teaching where dysphagia is considered an alarm symptom mandating gastroscopy. Thus, a trial of PPI can be considered both diagnostic and therapeutic. The significance of dysphagia however should not be minimised, as the condition is common, and the morbidity in terms of utilisation of healthcare and impairment in quality of life considerable.

Barium oesophagram (barium swallow) is the next investigation to consider after UGE, particularly when upper oesophageal anatomical or structural pathology is suspected (e.g. a pharyngeal pouch), or to exclude a major motility disorder (e.g. achalasia, spasm) when HRM availability is limited. Indeed, experts disagree when it comes to the sequence of the investigations, with some advocating barium swallow as the initial test in all, citing the ability to pre-plan endoscopic inventions such as dilatation, to avoid unnecessary repeated testing and to avoid potential risks including pharyngeal pouch perforation and aspiration in patients with suspected oropharyngeal dysphagia. Barium esophagography can also be considered when extrinsic compression is being considered, or when there is a strong suspicion of para-oesophageal (previously known is “rolling”) HH. Cross-sectional imaging may assist in some cases, with communication between reporting radiologists being imperative in this setting.

HRM is most useful when a motility disorder is suspected, or if a HH is thought to be contributing to refractory GORD and dysphagia. HRM is more accurate in the diagnosis of sliding HH, and is the gold standard for major disorders of peristalsis (achalasia, distal oesophageal spasm, jackhammer oesophagus and aperistalsis), demonstrating superiority over conventional manometry and barium studies.

The last decade has seen not only the advent of HRM, but also of intraluminal oesophageal impedance, and intraluminal oesophageal impedance planimetry (commercially known as Endoflip®). As well as being a measure of gastric reflux (alkaline and acid), IOI can detect bolus transit abnormalities. Many would argue that whilst this technology has proved of value to researchers, the clinical value is limited or yet unrealised. This assertion is based on data showing that impairment in bolus clearance defined by IOI correlates poorly with both the symptom of dysphagia.

### Table 3  Rheumatological causes of dysphagia

| Condition | Description |
|-----------|-------------|
| Scleroderma | Distal oesophageal dysmotility, part of the CREST syndrome |
| Sjogren’s syndrome | Xerostomia limits bolus lubrication and food passage, proximal oesophageal dysmotility |
| Rheumatoid arthritis | Proximal oesophageal dysmotility. Always consider and rule out associated cervical spine disease |
| Systemic lupus erythematosus (SLE) | Proximal oesophageal dysmotility |
| Degenerative cervical spine disease, surgery on the cervical spine and diffuse idiopathic skeletal hyperostosis (DISSH) | Anterior cervical osteophytes cause extrinsic compression of the oropharynx and proximal oesophagus |
and with manometric findings\textsuperscript{[28]}. Endoflip has only recently become available and can measure the hitherto unknown parameter of resistance to distension (distensability)\textsuperscript{[18]}. This technology has shown promise in assessing reduced distensibility in EoE and in postoperative measurement of achalasia response. On the other hand, inclusion of Impedance sensors with HRM has helped provide a visual impression of bolus transport or interruption, which is akin to radiology.

**TREATMENT**

Once a malignant process is excluded, the aims of treatment are to avoid aspiration or food bolus impaction, and minimise the morbidity associated with ongoing symptoms. Effective management of dysphagia obviously starts with early identification of the cause with judicious use of investigations. Requests for endoscopy for patients with oropharyngeal dysphagia where the risk of periprocedural aspiration is considerable and the utility questionable should ideally be preceded by an assessment of crico-pharyngeal function and speech pathologist evaluation of oral intake.

Proton pump inhibitors should be used when GORD is suspected as well as in cases of EoE to determine if this might be proton pump inhibitor responsive oesophageal eosinophilia (PPI-REE)\textsuperscript{[25]}. Patients with persistent eosinophilia will require swallowed topical corticosteroids (e.g., budesonide 1mg orally twice daily administered as an oral viscous solution) or an elimination diet\textsuperscript{[25]}. Specific treatment for oesophageal neoplasia is beyond the scope of this review and will depend on the extent of local invasion or occurrence of metastasis. The treatment of hypercontractile disorders of peristalsis may entail botulinum toxin injection of the distal oesophagus, and of achalasia might include pneumatic dilatation, or myotomy (surgical or peroral endoscopic myotomy (POEM))\textsuperscript{[8,9,38]}. Botulinum toxin injection will last only for a few months, and commonly requires repeated therapy\textsuperscript{[86,87]}. Surgical myotomy can result in durable improvement, whilst POEM may offer a less invasive approach, although long-term data is currently unavailable\textsuperscript{[88,89]}. Medications such as oral nitrates or calcium channel blockers lack efficacy but can be used as a holding measure while definitive therapy is being considered\textsuperscript{[87]}.

**CONCLUSION**

Dysphagia is a common symptom with a diverse range of aetiologies. In young healthy patients that do not describe additional red flag symptoms, a trial of PPI is reasonable and will result in symptomatic resolution in many cases. GORD can cause not only a decrement in peristaltic vigour, but may contribute to hyperalgesia, such that whilst food passes freely into the stomach, the patient experiences dysphagia indicating a somatosensory dysfunction. When further investigation is required, reconsideration of the site and the nature of symptoms (e.g., oropharyngeal vs oesophageal), and early recourse to upper gastrointestinal endoscopy is suggested, particularly given the increasing frequency of EoE and thus the need for oesophageal biopsies. HRM is required to exclude major disorders of peristalsis (achalasia, jackhammer oesophagus, distal oesophageal spasm and aperistalsis), although the finding of minor disorders of peristalsis is of unclear significance. Finally, gastroenterologists require a comprehensive knowledge of conditions that may cause or worsen dysphagia so that timely and efficient management occurs.

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