

Practical multidisciplinary framework for the assessment and management of patients with unexplained chronic aerodigestive symptoms

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ABSTRACT

Objective Patients experiencing unexplained chronic throat symptoms (UCTS) are frequently referred to gastroenterology and otolaryngology outpatient departments for investigation. Often despite extensive investigations, an identifiable structural abnormality to account for the symptoms is not found. The objective of this article is to provide a concise appraisal of the evidence-base for current approaches to the assessment and management of UCTS, their clinical outcomes, and related healthcare utilisation.

Design This multidisciplinary review critically examines the current understanding of aetiological theories and pathophysiological drivers in UCTS and summarises the evidence base underpinning various diagnostic and management approaches.

Results The evidence gathered from the review suggests that single-specialty approaches to UCTS inadequately capture the substantial heterogeneity and pervasive overlaps among clinical features and biopsychosocial factors and suggests a more unified approach is needed.

Conclusion Drawing on contemporary insights from the gastrointestinal literature for disorders of gut–brain interaction, this article proposes a refreshed interdisciplinary approach characterised by a positive diagnosis framework and patient-centred therapeutic model. The overarching aim of this approach is to improve patient outcomes and foster collaborative research efforts.

INTRODUCTION

Chronic throat symptoms, including cough, dysphonia, dysphagia, globus sensation and throat clearing, are frequently encountered in outpatient clinics.^{1–3} Differential diagnoses for these bothersome symptoms intersect multiple specialties, including otolaryngology, gastroenterology and respiratory medicine.^{4,5} However, identifying a definitive organic cause is often challenging for these symptoms, even with extensive evaluations.^{1,5,6}

Scenarios involving unexplained chronic throat symptoms (UCTS) present a dilemma for clinicians, as they contend with clinical ambiguity and unclear management

SUMMARY BOX

- ⇒ Unexplained chronic throat symptoms (UCTS) are a common presentation to gastroenterology and otolaryngology departments and cause considerable burden in both primary and specialist care.
- ⇒ The yield of diagnostic tests is low and the assessment and management of UCTS differs widely across specialty settings, involving contradictory aetiological concepts, nomenclature and terminology, fragmenting patient care, consequently leading to variable outcomes.
- ⇒ Clinical characteristics are non-specific and occur in heterogeneous fashion between diagnostic divides. Their correlation to postulated diagnoses remains unresolved, presenting a diagnostic and management dilemma for clinicians.
- ⇒ Key multifactorial pathophysiological concepts include chronic laryngopharyngeal inflammation, sensory and motor dysfunctions, symptom hyper-vigilance, intersected by diverse biopsychosocial factors, with significant overlaps with disorders of gut–brain interaction.
- ⇒ Evidence suggests a more unified symptom construct and interdisciplinary approach may offer advantages both for patient outcomes and collaborative research endeavours.

directions. Their aetiology and pathophysiology though widely postulated continue to have unresolved clinical correlations. Current research frequently polarises rather than unites, with conclusions confounded by diverse clinical taxonomies and specialty concepts.^{7,8} Consequently, cohesive, evidence-driven guidelines for UCTS remain absent.

There is no common terminology adopted for clinical presentations involving UCTS,⁹ which hinders precise prevalence estimates. Notwithstanding, UCTS is estimated to constitute a significant burden in primary care^{4,5} and often necessitate additional specialist evaluations.^{10–12} While often overlooked in the absence of clinical red flags,¹³



these symptoms are associated with significant morbidity, indicating a potentially under-recognised public health issue.^{14–17}

In response to this area of need, we assembled a collaborative team of otolaryngology and gastroenterology specialists with the goal of providing a concise appraisal of aetiological and pathophysiological concepts in this field, including existing terminologies and their clinical implications. A key objective was to review the evidence and outcomes of existing single specialty-led approaches to UCTS diagnosis and management.

Next, based on the findings of our review, we aimed to provide readers with a practical evidence-based framework for the assessment and management of UCTS presentations.

METHODOLOGY

A multidisciplinary team with diverse clinical backgrounds collaborated to define the objectives of this narrative review and synthesise the pivotal findings.

A comprehensive literature search was conducted using PubMed, Scopus and MEDLINE until June 2023. Keywords and MeSH terms pertinent to chronic aerodigestive symptoms were used. Manual citation analysis revealed additional pertinent studies. We evaluated original research, review articles, clinical trials and impactful editorials. Data concerning the clinical manifestations, patient characteristics, aetiological concepts, diagnosis and management approaches, and terminology related to UCTS were extracted and assessed. Authors independently assessed articles, collaboratively synthesised key findings and reached consensus. Findings are presented thematically, grouping related concepts and key insights to underscore complex interactions and challenges. Based on the review findings, a suggested evidence-based multidisciplinary biopsychosocial framework for UCTS was developed incorporating aetiological perspectives and encompassing multifaceted symptom influences.

UCTS: EPIDEMIOLOGY AND PUBLIC HEALTH IMPORTANCE

Chronic throat symptoms listed in [table 1](#) encompass persistent complaints (>8 weeks) related to the throat, upper airway, voice or swallowing. Given the complex interactions between the aerodigestive structures and the symptom heterogeneity, multidisciplinary engagement is often necessitated.^{1–3} Differential diagnoses span various aerodigestive lesions and other structural pathologies ([table 2](#)). Typically, distinctive symptom insights within organic disease frameworks facilitate a targeted assessment strategy for the undifferentiated patient, which is influenced by presenting symptoms and pertinent patient factors such as medical history and smoking status. These relationships expedite the exclusion of malignant diseases, steering investigations towards the most relevant aetiological considerations, which permits efficient care across diverse specialty realms.

UCTS describe the scenario when no clear organic or structural pathology is identified despite thorough evaluations of the presenting complaints. The lack of standardised terminology for UCTS complicates accurate prevalence estimates.⁹ [Table 3](#) summarises prevalence data reported for individual symptoms, alongside the proportion of cases labelled ‘idiopathic’ or ‘functional’ after investigation. These data suggest that no discernible structural pathology is evident in 31–93% of UCTS presentations, depending on the symptom and assessment method. Given the high prevalence of chronic throat symptoms in general populations, this supports estimates that UCTS may collectively account for 5–10% of total primary care visits⁵ and precipitates significant numbers of referrals to otolaryngology, gastroenterology, respiratory and other specialty departments.^{4,5} However, inconsistent terminology for ‘non-organic’ throat symptoms and limited examinations may understate their true prevalence. While UCTS are generally considered benign, growing evidence of their impact on quality-of-life^{14–17} indicates a public health significance that may be under appreciated.

Table 1 Chronic throat symptoms encountered in primary care and specialist outpatient centres

Symptoms	Clinical red flags	Patient red flags
Cough	Progressive symptoms	Smoker or ex-smoker
Dysphonia	Regurgitation of undigested foods	Immunosuppression
Globus sensation	Odynophagia	Prior head and neck cancer
Oropharyngeal dysphagia	Haemoptysis	Prior head and neck radiation
Repetitive throat clearing	New dysphagia	History of skin cancer
Catarrh/sensation of mucus in the throat	Airway limitation symptoms	Prior haematological malignancy
Abnormal throat sensations	Weight loss	History of respiratory cancer
	Constitutional symptoms	History of oesophageal cancer
	Bone pain or generalised aches	History of Barrett’s oesophagus
	Palpable or radiological thyroid mass or nodule	
	Palpable or radiological lymphadenopathy	

Table 2 Structural and pathological causes of chronic throat symptoms

Structural disease	Oesophageal pouch/diverticulum Oesophageal web Mediastinal tumours Lymphoma Eagles' syndrome Cricopharyngeal spasm Intrusive cervical osteophytes	Laryngeal dystonia Guillain Barre syndrome Myasthenia gravis Spasmodic tremor Motor neuron disease Muscular dystrophy Cerebral palsy	Systemic disease	Nitrates Calcium channel blockers Opioids ACE inhibitors Bisphosphonates Anticholinergics
Malignant lesions of the aerodigestive tract Benign lesions of the aerodigestive tract Tonsillar hypertrophy Pharyngeal diverticulum Reinkes oedema Vocal cord palsy Fixed larynx Laryngeal trauma Pharyngeal web Candidiasis			Sjogren syndrome Systemic lupus erythematosus Mixed connective tissue disease Rheumatoid arthritis Systemic sclerosis Wagner's Hypothyroidism Amyloidosis Relapsing polychondritis Sarcoidosis Epidermolysis bullosa Pemphigoid Angioneurotic oedema	Iatrogenic Head and neck surgery Head and neck radiation Intubation trauma Non-invasive ventilation
Regional disease	Neurological disease	Respiratory disease		
Thyroid nodules or goitre Neck masses (benign and malignant) Neck cysts (benign and malignant) Cervical lymphadenopathy	Stroke (including brainstem infarcts with bulbar involvement) Parkinson's disease CNS tumour Amyotrophic lateral sclerosis Multiple sclerosis Polymyositis Myotonic dystrophy Bulbar palsy	Asthma (and variants) Allergic rhinitis Rhin sinusitis Restrictive lung disease Bronchiectasis Chronic bronchitis Eosinophilic bronchitis Bronchogenic cancer Tuberculosis Cystic fibrosis Primary ciliary dyskinesia	Medications	
			Tricyclic antidepressants Potassium supplements NSAIDs	

ACE, angiotensin-converting enzyme; CNS, central nervous system.

Table 3 Epidemiology of chronic throat symptoms

Chronic throat symptom	Prevalence (general populations)	Per cent of cases without organic disease cause
Cough	2–18% ¹¹³	42% ¹¹³
	10% ¹⁵⁵	37% ¹⁵⁵
	12.5% ¹⁵⁶	
	8.2% ¹⁵⁷	
	2.5% ¹³⁵	
Dysphonia	7.6% ¹⁵⁸	42.5% ⁴⁷
	3–15% ⁴⁷	43.7% ⁶
	6.6–7.5% ⁶	60% ¹⁵⁹
	10% ⁴⁸	31% ⁴⁸
Globus sensation	45% ¹¹⁰	86–90%
	12.5% ¹¹⁴	92.6% ¹⁶⁰
	22% ¹⁶¹	
	26.48% ¹²⁹	
Oropharyngeal dysphagia	40% ¹⁶²	51–21% ¹⁶³
	16.4% ¹⁶⁴	58% ¹⁶⁵
	22% ¹⁶⁶	3.2% ¹⁶⁷ (incidence of functional dysphagia in general population)
	13% ¹⁶⁸	
	43.8% ¹⁶⁹	
	20% ¹⁷⁰	
Catarrh/mucus sensation	ND	ND
Repetitive throat clearing	ND	ND
ND, no data.		

DIAGNOSTIC AND CLINICAL CLASSIFICATIONS OF UCTS

Several aetiological theories have emerged over decades of scientific enquiry to account for UCTS and inform divergent diagnoses and treatment approaches employed for these complaints. These may be broadly divided into chronic inflammatory and functional symptom concepts, the prominent theories and diagnoses of which are summarised below.

Chronic inflammatory concepts

Occult irritation of the aerodigestive tract causing chronic inflammation of the larynx or laryngopharynx is promoted as a cause of non-specific UCTS. Potential contributors include refluxed gastroduodenal content, inhaled irritants, respiratory allergens and voice behaviours. However, inflammatory indicators from nasoendoscopy¹⁸ are non-specific to both symptoms and postulated inflammatory aetiology in most literature investigating this relationship,^{3 5 8 19} are often identified in asymptomatic individuals²⁰ and are subject to variable interpretations, highlighting diagnostic complexities.

Gastro-oesophageal reflux disease

Laryngopharyngeal reflux (LPR) is theorised to result from the back flow of gastroduodenal contents into the laryngopharynx, leading to chronic inflammation.^{21–23} Central to its pathophysiology is the inflammatory reaction to these contents, with pepsin being a primary culprit.^{24–27} Although gastro-oesophageal reflux disease (GORD) is more prevalent among those with chronic throat issues,³ attributing aerodigestive symptoms to LPR is contentious.^{1 22 28–30} Unlike GORD, reflux-associated throat symptoms are non-specific,¹ often seen in upright individuals during the day, regardless of BMI, and typically without heartburn.⁴



Diagnostic approach

Diagnosing LPR is complex. Nasoendoscopic findings reflect secondary mucosal inflammation and are open to interpretation.^{5 7 19 21} The gold standard for GORD diagnosis, intraluminal oesophageal pH-impedance (pH-II), has poor sensitivity and specificity for LPR, offering little therapeutic guidance.^{28 31–34} The search for a definitive diagnostic tool for LPR continues, making the current diagnosis largely clinical.

Treatment approach

Treatment often mirrors those used in treatment of GORD, emphasising lifestyle changes although their effectiveness has yet to be validated. Proton pump inhibitors (PPIs) were once the go-to for LPR, but recent studies question their efficacy for reflux-induced laryngeal symptoms,^{35–38} possibly due to the role of pepsin. Liquid alginates consumed after meals may have modest benefits based on early research.^{39 40} Anti-reflux surgery appears to be more effective than acid suppression therapies,^{22 41–46} but its symptomatic relief does not always correlate with acid and impedance metrics,^{33 43} leading to varied interpretations in the literature and challenges in patient selection.

Vocal demand and voice behaviour

Dysphonia and other irritating throat symptoms are more prevalent among professional voice users⁶ due to prolonged or exaggerated vocal fold vibration, which cause mechanical epithelial injury and inflammation, termed phonotrauma.^{47–53} Laryngeal muscle tension and fatigue related to excess vocal strain may play a role^{7 10 54–56} and contributions from psychosomatic factors are common themes in the literature.^{10 48 57–60}

Diagnostic approach

A history of increased voice demand is sought although chronic phonatory symptoms (cough and throat clearing) are also considered potential precipitants.⁶¹ Nasoendoscopic findings involving laryngeal inflammation, motor tension or disrupted vocal cord movement may be contributory although such features are non-specific.^{7 62}

Treatment approach

Treatments include strategies to improve vocal hygiene and minimise excess voice demands, as well as targeted therapies to normalise aberrant motor patterns or tension^{63–65} and address sensory components which may drive phonotraumatic symptoms.^{66–68} Patients may also be provided with reflux therapies in a ‘cover all’ approach.

Aerosolised irritants

Numerous airborne aerosols are irritative or noxious to the respiratory tract, including the laryngopharynx.^{47 52 69–74} Irritants are classified by occupational, domestic and environmental source. Impacts on the aerodigestive tract are specific to irritating agents and are associated with several throat symptoms.

Diagnostic and treatment approach

Comprehensive analysis of environmental aerodigestive irritants and proposed aerodigestive symptom implications are available, including diagnostic and therapeutic strategies.^{52 70 73}

Respiratory allergy

Allergic rhinitis (AR) and asthma are among the most common allergic manifestations in the general population.^{75 76} Despite a continuous respiratory epithelium extending between the nasal and lower airways,⁷⁵ the larynx and pharynx are excluded among defined airway allergy phenotypes.^{75 77} Chronic throat symptoms are more prevalent in allergic populations^{78–80} and vice versa.⁸¹ Historically, throat symptoms when present are regarded as secondary manifestations, caused by irritative secretions travelling up from the lower airway or falling from the nasal cavity or via unified airway pathophysiology.^{82–86} However, emerging evidence advances IgE-mediated eosinophilic inflammation within the laryngopharynx as a previously under-recognised consequence of allergen sensitisation in some.^{77 83 87 88} This concept of an ‘allergic laryngitis’ (AL) is supported by a developing literature that points to epidemiological evidence and results from direct allergy provocation studies in both animal and human studies.^{80 87 89} Further research is needed to clarify its biological basis and clinical implications.

Diagnostic and treatment approach

AL is yet to be accepted as a valid diagnosis of airway allergy and has no established diagnostic or treatment directions beyond chronic cough under the ‘upper airway cough syndrome’ framework.

Functional throat disorders (FTD)

Throat symptoms appear to, in some cases, reflect patterns of abnormal aerodigestive sensation, motility and/or reflex function.^{11 90} These physiological disruptions to usual function are proposed to account for varied symptom presentations in patients without structural disease.

Sensory disruptions

Hypersensitisation of aerodigestive structures is a common theme among symptom theories related to UCTS.^{11 15 51 66 91–98} Cough hypersensitivity syndrome (CHS) and laryngeal hypersensitivity and diagnoses which typify this pathophysiological pattern, reinforced by emerging research.^{10 15 22 51 66 71 91 92 97–103} The core understanding implicates sensory dysregulation of aerodigestive tract or related reflexes in symptom emergence, most notably cough and globus sensation.^{92 104–108} Postulated mechanisms encompass epithelial sensory receptor adaptations in response to chronic inflammation or other stimuli,⁹⁰ somatosensory adaptations involving the vagus nerve or higher centres involved in neuromotor regulation of the aerodigestive tract.^{95 109}



Motor disruptions

Beyond sensory dysfunction, dysregulated motor patterns impacting the laryngeal or supraglottic musculature are detected during laryngoscopic evaluations in patients with UCTS.^{10 54–56} Two predominant phenotypes emerge: vocal cord dysfunction syndromes that, barring inducible laryngeal obstructions, do not compromise respiratory function; and muscle tension syndromes, particularly concerning the supraglottic musculature. Manifestations include a spectrum of chronic throat symptoms, with dysphonia, globus, throat clearing and cough often highlighted.¹¹ Oropharyngeal dysphagia and globus sensation are likewise proposed to show association with motor tone or coordination dysfunctions affecting the upper oesophageal sphincter or proximal oesophagus.^{41 110–112}

Aetiology of FTDs

The aetiology of sensory and motor dysfunctions in FTD remains elusive. Associations encompass psychosomatic factors, central adaptations, personality, gender, trauma, chronic pain, overlapping functional gastrointestinal disorders now considered as disorders of gut–brain interaction (DGBI), viral infections, microbiome and prolonged inflammatory stimuli of various sorts.^{11 89 97 109 113–115} CL is identified as a key risk factor for physiological changes proposed to underlie functional symptoms, and sensory and/or motor changes may themselves predispose patients to chronic laryngitis through various mechanisms. Differentiating inflammatory from functional causes is therefore challenging among intertwined pathophysiological relationships.^{13 51}

Diagnostic approach

Diagnoses that identify sensory or motor changes as the cause of symptoms in UCTS are numerous. They may relate to specific symptoms (eg, CHS), refer to postulated symptom mechanisms (eg, laryngeal dysfunction), or a combination thereof (eg, muscle tension dysphonia). Diagnostic approaches vary but typically couple symptom and patient factors with functional disruptions on a clinical basis after organic disease exclusion, occasionally incorporating nasoendoscopic findings.

Treatment approach

Treatments for FTD restore normal sensory and motor aerodigestive functions and may directly target potential precipitants or symptoms. Non-pharmacological interventions include sensory and motor rehabilitation programmes⁶³ and other behavioural interventions.^{116 117} On the pharmacological front, neuromodulators and antidepressants may mitigate sensory and motor irregularities^{15 64 67 85 91 118} and bolster normal functions by addressing central adaptations and psychosomatic factors.^{10 11 59 119}

Biopsychosocial interactions in UCTS

The aerodigestive tract is an intricate physiological structure. Its optimal function hinges on the sophisticated interplay of somatosensory feedback, central processing

and coordinated motor responses.^{28 58 104 108 120–124} This interplay is mediated through dense vagal networks linking the aerodigestive structures with regulatory centres in the brain stem and cortex, which are enhanced by voluntary somatic inputs.^{57 101 125 126} In addition, locoregional organ feedback and disease states influence function through unified airway and oesophagobronchial mechanisms.^{108 127 128} The aerodigestive mucosa is unique in its exposure to inhaled air with variable temperature, humidity and particulate content; endogenous secretions; and diverse ingested materials. Various biopsychosocial factors (figure 1) further modulate its function and are yet to be fully explored (figure 1).^{91 113 129–133} The complex potential for interaction among these factors in the generation of UCTS is outlined in figure 2 and is reminiscent of those that characterise DGBI.

TAXONOMY AND TERMINOLOGY OF UCTS AND RELATED DIAGNOSES

UCTS involves diverse symptom presentations, in the absence of structural causes, and encompasses divergent aetiological theories and specialty approaches. This clinical dilemma is the subject of highly divided terminology and taxonomy, involving specialty and regional divides and presents a challenge in developing consistent clinical guidelines. Divisions reflect varying interpretations of symptom mechanisms, origins and significance, as detailed above.

In table 4, diagnoses and other labels relevant to UCTS in the literature are presented and categorically divided according to inflammatory and functional concepts. Terms with a shared clinical or pathophysiological focus are further grouped. Current understanding of clinical features, symptom mechanisms, disease associations and other identified biopsychosocial factors for each were synthesised from the literature and are summarised in the table. Similarly, biopsychosocial associations associated with each UCTS reported in the literature are summarised in table 5.

On review of the literature, three broad themes emerged in terms of diagnostic taxonomy and nomenclature:

Symptom-centric terms

Various diagnoses in the UCTS landscape identify a predominant symptom profile following the exclusion of structural pathologies (eg, idiopathic cough, functional dysphonia). This extends the symptom-directed approach that guides the assessment of organic and structural disease concepts in patients with undifferentiated throat symptoms.

Mechanism-centric terms

Diagnoses may identify a central mechanism for UCTS and likewise imply the absence of identifiable organic disease. They may relate to single symptoms (eg, CHS, muscle tension dysphonia) or encompass multiple symptom manifestations (eg, Laryngeal dysfunction).

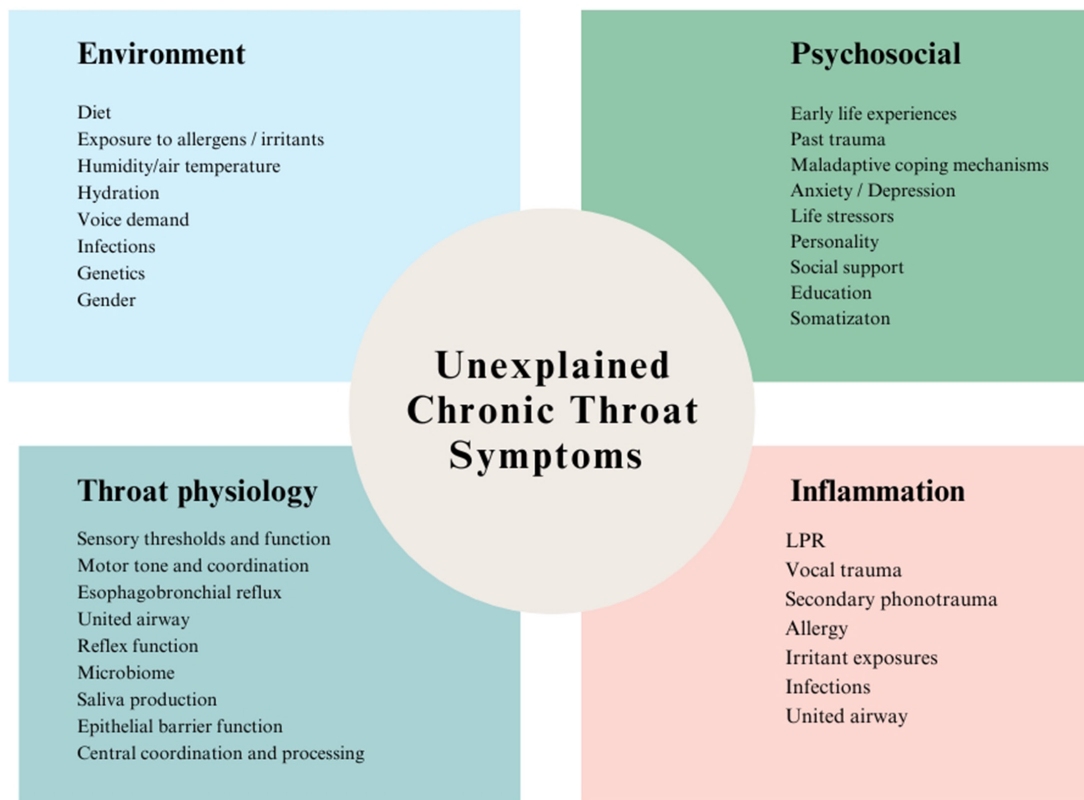


Figure 1 Biopsychosocial influences in unexplained chronic throat symptoms. LPR, laryngopharyngeal reflux.

Disease-centric terms

UCTS may be empirically attributed to consequences of underlying disease states, such as reflux or allergy (LPR, AL). These diagnoses are distinguished from those in table 2 by the inherent challenge in both identifying the proposed disease and establishing the symptom–disease correlation.

Are existing clinical classifications and divisions of UCTS substantiated?

We assessed whether the diagnostic and descriptive divisions outlined table 4 correspond to substantiable clinical phenotypes or populations, separable by defined clinical criteria, investigation findings or biopsychosocial factors. Our literature review summarised in tables 4 and

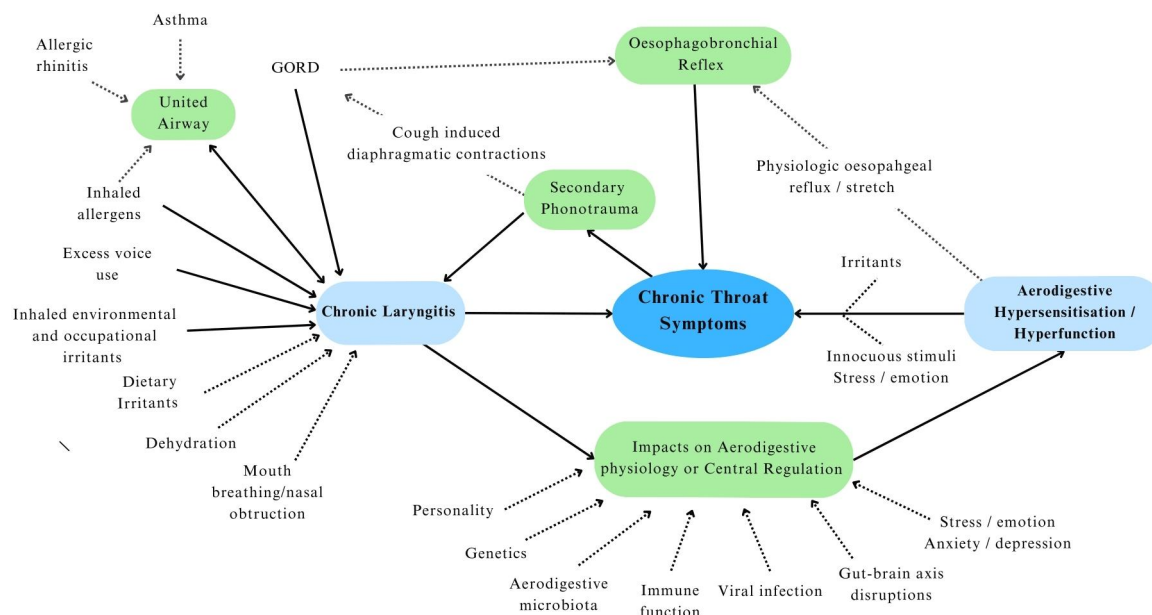


Figure 2 Biopsychosocial model of unexplained chronic throat symptoms. GORD, gastroesophageal reflux disease.

Table 4 Clinical features reported in association with unexplained chronic throat symptoms

	Chronic inflammation— chronic laryngitis (CL)				Functional throat disorders (FTD)		
Common pathophysiology	Chronic non-eosinophilic inflammation of the ADT				Chronic eosinophilic inflammation of the ADT	Abnormal sensory or motor function within the ADT or components, without clear organic disease correlates	
Aetiology	GORD	Aeorsolised irritants	Voice behaviours	Aerosolised allergens	Aerodigestive sensory/reflex dysfunction	Aerodigestive motor dysfunction	
Diagnoses	LPR, EER, RL	OL, WAL, WUACS, WAILS, OCS	VA, VTL, SD, MTD	LA, AL	ILS, LH, SLN, LD, CHS, ICC, RCC, GP	LD, MTD, FD, LHS, UESD, CPS, VCD, PVFM, STD	
Reported symptoms							
Cough	++	++	++	++	++	++	
Dysphonia	++	++	+++	++	++	++	
Dysphagia	+	+	+	+	++	+++	
Globus	++	+	+	+	+++	++	
Paraesthesia	++	++	++	++	+	+	
Throat clearing	++	++	++	+++	++	++	
Reported nasoendoscopic findings							
Features of mucosal inflammation	++	++	++	++	++	++	
Vocal cord dysfunction	+	+	++	+	++	++	
Abnormal muscle tone or coordination	++	++	+++	++	+++	+++	
Sensitive and specific clinical findings or biochemical markers	No	No	No	No	No	No	

AL, allergic laryngitis; CHS, cough hypersensitivity syndromes; CPS, cricopharyngeal spasm; EER, extraesophageal reflux; FD, functional dysphonia; GORD, gastro-oesophageal reflux disease; GP, Globus pharyngeus; ICC, idiopathic chronic cough; ILS, irritable larynx syndrome; LA, laryngeal allergy; LD, laryngeal dysfunction; LH, laryngeal hypersensitivity; LHS, laryngeal hyperfunction syndromes; LPR, laryngopharyngeal reflux; MTD, muscle tension dysphonia; OCS, occupational cough syndrome; OL, occupational laryngitis; PVFM, Paradoxical vocal fold movement (excluding inducible laryngeal obstruction); RCC, refractory chronic cough; RL, reflux laryngitis; SD, Singers dysphonia; SLN, superior laryngeal nerve neuropathy; STD, supraglottic tension dysphonia ; UESD, upper oesophageal sphincter dysfunction; VA, vocal abuse; VCD, vocal cord dysfunction; VTL, vocal tension laryngitis; WAILS, Workplace associated irritable larynx syndrome OCS ; WAL, workplace-associated laryngitis; WUACS, Workplace upper airway cough syndrome .

5 revealed poor performance and specificity of current symptom-centric, mechanism-centric and disease-centric labels, with considerable overlapping symptom profiles and clinical features across the common diagnostic

categories for UCTS. Furthermore, symptoms were found to rarely occur in isolation, despite their division through varying diagnostic concepts.^{99 134} Present taxonomic approaches and related terminology were

Table 5 Symptom associations in unexplained chronic throat symptoms

Associations	Cough	Dysphonia	Globus	Dysphagia
Female gender	++	++	+++	+
Anxiety/depression	++	++	+++	+++
Professional voice use	++	+++	++	+
Environmental irritants	+++	++	++	-
GORD	+++	+++	+++	++
Allergy	++	++	++	+
Vocal cord dysfunction	++	++	++	++
Supraglottic tension	++	++	+++	+
Chronic laryngitis	+++	+++	++	++

GORD, gastro-oesophageal reflux disease.



therefore found to reflect a dualistic, 'all-or-nothing' diagnostic paradigms, which appeared not to recognise the extensive clinical heterogeneity and shared multifactorial biopsychosocial influences. The absence of clear structural pathology diminishes the predictive power of symptom indicators, which, in tandem with variations in clinician approach, specialty perspectives and symptom interpretations, complicates the establishment of uniform assessment and management protocols. Our review has highlighted a consequent divergence in diagnostic and therapeutic approaches across specialties.^{5 7 8} This may contribute to fragmented care, patient dissatisfaction and anxiety,¹³⁵ and increased healthcare resource use as clinicians' resort to repeated and often overlapping investigations in pursuit of diagnostic or treatment direction.

The case for a more unified approach to UCTS

In a study involving 344 prospective patients with UCTS, no association was found between symptoms and nasoendoscopic features.⁵ In addition, attempts to define distinct patient subgroups through assessment of clinical, demographic and biopsychosocial factors have been unsuccessful.⁵ This notable finding aligns with the qualitative assessment presented here, highlighting the indistinct boundaries among UCTS presentations and strongly suggests the need for a more holistic and unified perspective. Recurrent themes involving inflammatory stimuli, psychosomatic influences, aerodigestive sensitisation and motor disruptions and overlap with other functional disease syndromes are consistent in the literature surveyed. A syndrome-based perspective offers the potential for a comprehensive framework that captures the diverse manifestations of UCTS and is substantiated by increasing support in the literature.^{4 5 59 134} This shift may pave the way for holistic, patient-centric research and therapeutics that encompass multifactorial influences on symptoms.

This collaborative review has highlighted several important themes and challenges related to UCTS, drawn from the relevant specialty literature. Our review has highlighted that UCTS profoundly affects patients' well-being. The widespread division among varied terminologies and specialty perspectives may underestimate its prevalence and public health impact. Such symptoms, when persistent, commonly drive primary care visits and negatively impact patient quality of life.

Moreover, the non-specificity of UCTS has proven to be clinically challenging. Although clinical phenotypes may be present and offer potentially valuable therapeutic directions, the present reliance on symptom characteristics for diagnosis may mislead clinicians who extrapolate symptom meanings applicable within structural and organic symptom frameworks. While definitions for non-structural throat complaints continue to develop and evolve across specialty literature, this review highlights the limitations of these often unilateral, single specialty approaches. The absence of a

unified symptom language and minimal interdisciplinary collaboration in both clinical and scientific contexts have hampered progress.

Our review highlighted that the diagnostic approach often varies based on specialty perspectives, leading to inconsistent treatment plans. The inability to link UCTS to objective disease markers makes establishing causality difficult. Because of the non-distinct nature of these symptom presentations, responses to varied therapeutic interventions are inconsistent and differ significantly among patients. This indicates an intricate pathophysiology not completely represented by current diagnostic approaches. Finally, our review highlighted the significant overlap between DGBI and UCTS involving complex aerodigestive sensorimotor dysfunction, symptom hypervigilance and complex biopsychosocial interactions.

Are UCTS part of a spectrum of DGBI?

It is clear from the findings of our review that the profile of UCTS closely mirrors functional gastrointestinal disorders, now classified as DGBI, with symptoms not explained by structural abnormalities, redundant tests, multifactorial pathophysiology and stigmatisation, resulting in patient dissatisfaction and inflated healthcare costs.¹³⁶

Current approaches to the diagnosis and management of UCTS are rooted in dualistic aetiological theories, resulting in fragmented diagnoses and inconsistent treatments. However, within gastroenterology, the introduction of the Rome IV DGBI criteria has marked an important shift. Modern evidence from DGBI literature has evolved to refute simplistic mind-body dualistic notions,¹³⁷ instead uncovering characteristic and complex physiologic disruptions in these patients, even if a biochemical marker or structural aberrations cannot be readily represented.^{114 138 139}

The Rome IV criteria unify previously disparate diagnoses by focussing on symptom clusters and multi-dimensional clinical profiles, as opposed to speculative aetiological theories, streamlining the diagnostic process and promoting efficient delivery of effective therapy for patients.¹³⁹ They underscore the importance of interdisciplinary collaboration in DGBI management, integrating the expertise of gastroenterologists, dietitians, psychologists and primary care physicians. This holistic approach recognises the intricate interplay of biological, psychological and social factors, promotes enhanced patient outcomes and empowers and fosters healthcare efficiency by reducing superfluous tests and expediting interventions.¹⁴⁰⁻¹⁴⁴

The structured DGBI framework has also spurred significant research advances through the adoption of a common language for 'non-organic' gastrointestinal symptoms, deepening the understanding of epidemiology, pathophysiology and evidence-based treatments in this field, ultimately optimising patient care.

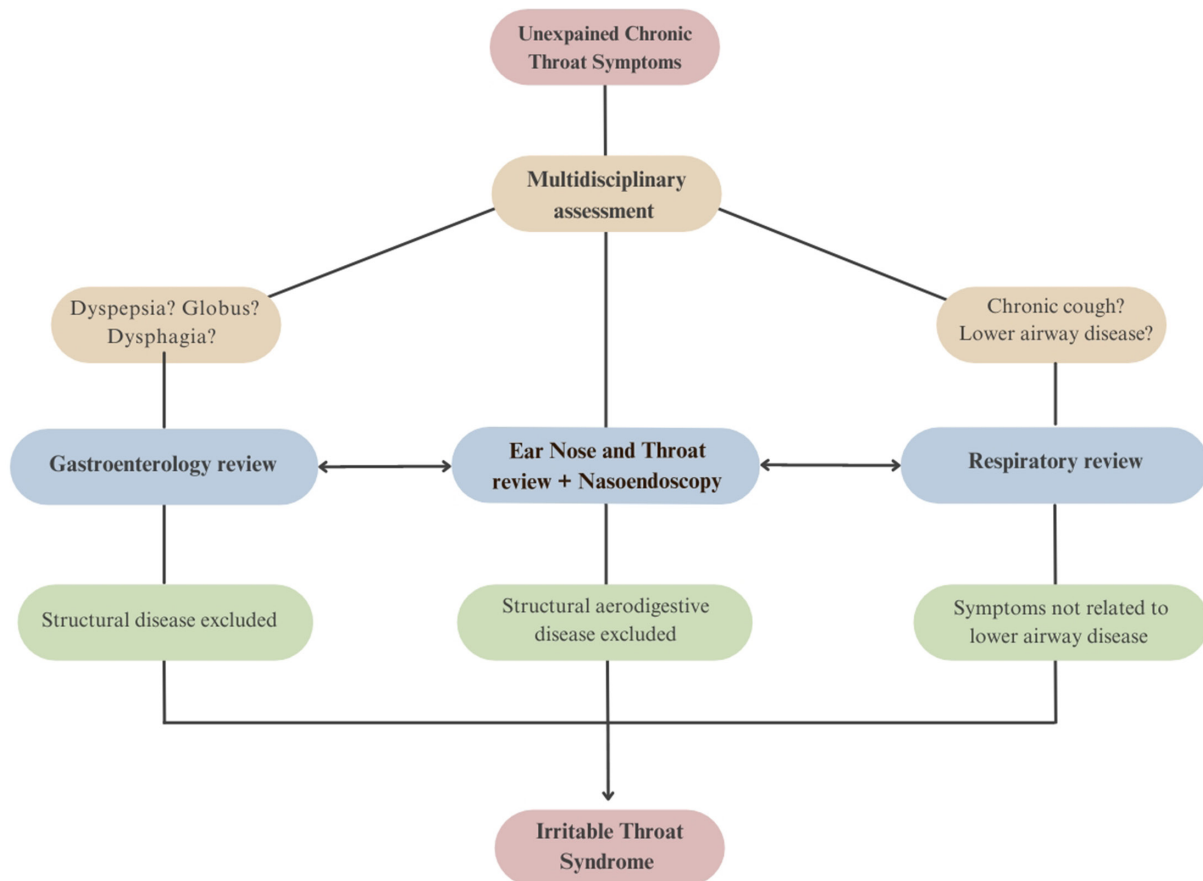


Figure 3 Suggested approach for a positive diagnosis of irritable throat syndrome.

Transferring insights from gastroenterology towards a comprehensive approach to UCTS

Inspired by these transformative strides within DGBI and gastroenterology, there is a compelling case for adopting a similar paradigm in UCTS. The potential benefits of translating this approach to UCTS include:

► Diagnostic clarity

A structured, symptom-focused diagnostic criteria may unite divided practice, validating and authenticating patient experience through adoption of a positive diagnostic strategy. A cohesive system would demystify diagnoses for both patients and clinicians reduce ambiguities and enhance patient trust in the diagnostic journey.

► Multidisciplinary collaboration

An integrated collaborative stance incorporating multidisciplinary specialist and allied health expertise can offer a comprehensive perspective, ensuring that all aspects—physical, physiological, psychological, and social—are considered.

► Comprehensive care strategies

Adopting a biopsychosocial care model promotes holistic, patient-focused treatments, which may improve outcomes and enhance patient satisfaction.

► Efficient care delivery

Streamlined approach may minimise redundant tests, reduce hospital visits, expedite symptomatic treatments, and reduce healthcare costs.

► Research impetus

Stimulate collaborative research endeavours, deepening understanding of its aetiology, treatments, and potential prevention strategies.

'Irritable throat syndrome' as a unifying concept

Our findings suggest that there is a pressing need for an updated multidisciplinary strategy for patients presenting with UCTS. While current Rome IV diagnostic criteria for oesophageal DGBI do incorporate some patients with UCTS under globus and functional dysphagia criteria,¹⁴⁵ this review article has highlighted the need to broaden the spectrum given the breadth and heterogeneity of symptom presentations of patients with UCTS. A model for such an approach, under a proposed 'irritable throat' framework, is outlined here (figure 3), drawing on the key findings of this collaborative review of literature while incorporating existing Rome IV diagnostic criteria for globus and functional dysphagia.¹⁴⁵

The term 'irritable throat syndrome' (ITS) appears variably in the literature, with inconsistent definitions.^{52 57 59 68 71 146} The term is advantageous because of its simplicity, clear anatomical correlations and parallels to the well-accepted Rome criteria for irritable bowel syndrome. Our findings suggest that this term could be repurposed through a broadened and interdisciplinary construct for patients with chronic throat symptoms that are inadequately explained by structural abnormalities,

**Box 1 Proposed diagnostic criteria for irritable throat syndrome**

Presence of one or more of the following unexplained chronic throat symptoms; cough, dysphonia, globus sensation, oropharyngeal dysphagia, repetitive throat clearing, catarrh/sensation of mucus in the throat, abnormal throat sensations, for at least 1 day each week, over the last 12 weeks, with:

- No explanation from comorbid diagnoses.
- No explanation from routine physical examinations and investigations.
- Exclusion of structural or other organic pathology of the aerodigestive tract via nasoendoscopy.

Additional criteria

- Patients with PPI refractory reflux symptoms:** Throat (extra-oesophageal) symptoms persist despite standard GORD therapies. In patients with PPI-resistant reflux/dyspeptic symptoms (in addition to throat symptoms), gastroenterology evaluation excludes structural gastrointestinal abnormalities and objective evidence of pathological gastro-oesophageal reflux.
- Patients with globus sensation:** Exclusion of a structural lesion identified on physical examination, laryngoscopy or endoscopy, absence of a gastric inlet patch in the proximal oesophagus, exclusion of a major oesophageal motor disorder and exclusion of eosinophilic oesophagitis. If overlapping PPI refractory oesophageal reflux symptoms consider oesophageal pH studies to exclude pathological gastro-oesophageal reflux.
- Patients with overlapping oesophageal dysphagia:** Gastroenterology evaluation excludes structural oesophageal causes, eosinophilic oesophagitis and major oesophageal motor disorders.
- Patients with lower airway disease:** A respiratory physician confirms that refractory throat symptoms cannot be adequately explained by comorbid lower airway pathology.
- Patients with chronic cough:** A respiratory physician excludes organic lower airway causes of cough.

GORD, gastro-oesophageal reflux disease; PPI, proton pump inhibitor.

believed to result from complex interactions between biopsychosocial factors.

Establishing a positive diagnosis: suggested criteria for 'irritable throat syndrome'

The pursuit of a positive diagnostic paradigm has standardised the approach to DGBI and permitted clinicians to proactively pursue a diagnosis based on defined symptom clusters, after excluding mimics. Based on our findings, we propose that a similar evidence-based model might be adopted for a positive diagnosis in patients with irritable throat-like symptoms following evaluation of chronic throat symptoms to rule out discernible structural causes and mimics (box 1). This positive diagnosis framework offers a structured approach, eliminating the need for repetitive and usually unremarkable tests. Further, it supports the adoption of a common medical language to validate patient symptoms, standardise interdisciplinary approaches, strengthen patient–clinician rapport,

promote prompt delivery of therapy and encourages judicious use of resources.

Rationale for an updated treatment approach for patients with irritable throat-like symptoms

In DGBI, a holistic approach addressing biopsychosocial factors has been shown to be superior to single specialist-led care.¹⁴¹ This multidisciplinary model centres on the patient, enabling tailored treatment pathways through collaboration. We propose extending this model to include irritable throat symptoms. Depending on the patient's symptom profile, optimal care for refractory irritable throat-like symptoms may require collaboration between otolaryngologists, gastroenterologists, respiratory specialists, speech therapists, psychologists and others, addressing the full range of biopsychosocial factors implicated in UCTS.

The key goals of this treatment approach include:

- Validating the impact of symptoms on patient well-being and providing education and reassurance.
- Promoting education and strategies to enhance aerodigestive tract health and overall patient well-being, which encourages patient participation in symptom management.
- Thorough assessments to individualise treatment goals and strategies according to patient needs.
- The regular evaluation of symptom progression to refine treatment strategy.
- Open communication within a multidisciplinary team, especially for complex cases.

The evidence base for current therapeutic targets for irritable throat-like symptoms synthesised from our literature review to inform a suggested evidence-based treatment framework (figure 4) is summarised in the online supplemental table.

This evidence-based framework involves a stepwise progression of the therapeutic strategies below.

- Standard therapies and education:** Patient education to optimise habits for aerodigestive health, reassurance surrounding long-term symptom implications and preliminary speech therapies for primary symptom concerns.
- Psychosocial interventions:** Patients with comorbid anxiety and depression or who report elevated psychological stress are offered interventions to support mental well-being, relaxation and decreased symptom hypervigilance.
- Assessment and treatment of potential inflammatory causes:** Considers targeted interventions for reflux, allergy, voice behaviour and environmental/occupational exposures.
- Empirical trial of neuromodulators and other sensory targeted therapies:** Offered for persistent symptoms in suitable candidates.
- Objective reflux quantification:** Indicated for patients with refractory symptoms despite maximal non-invasive therapies, where a defined high reflux

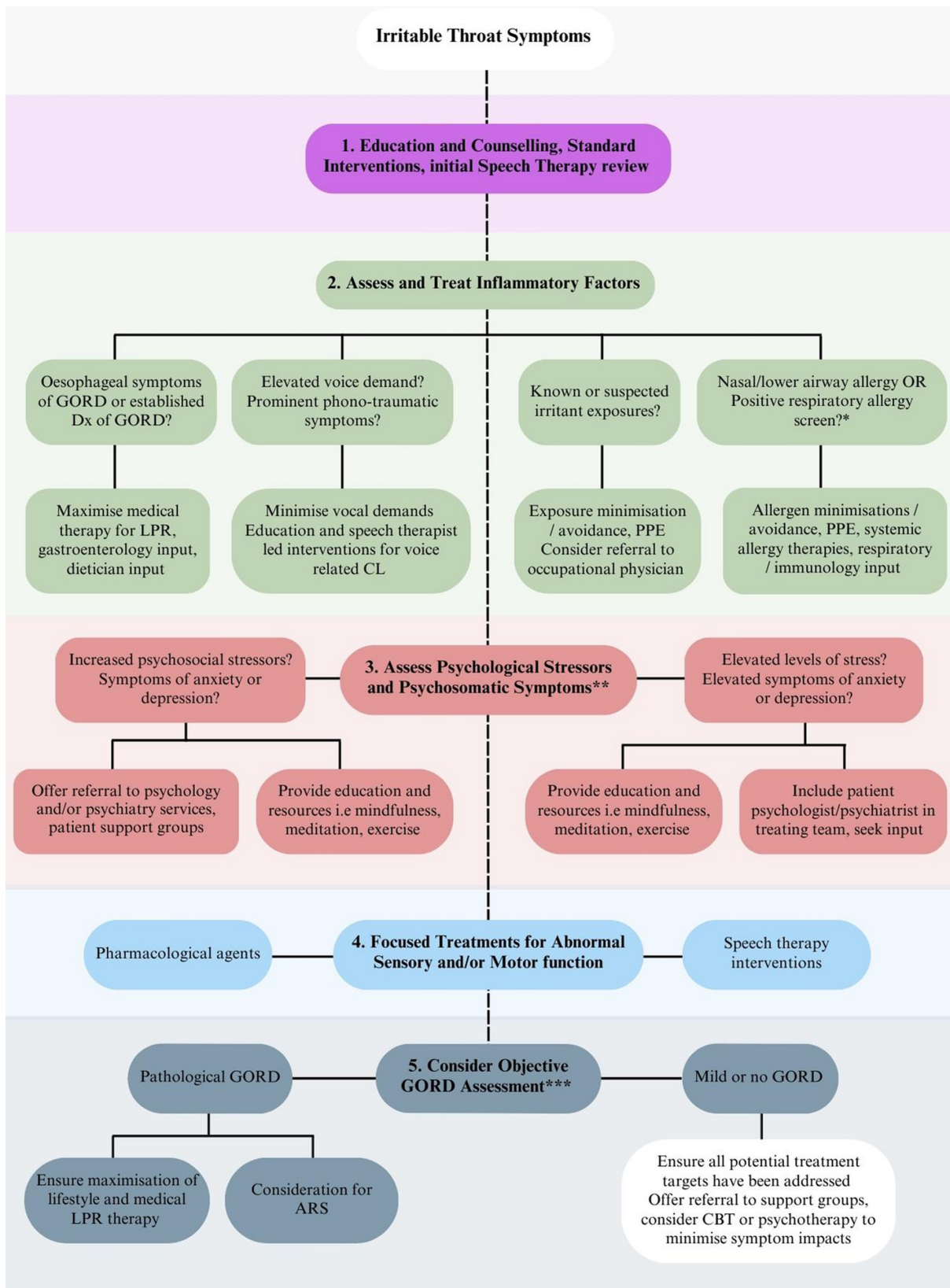


Figure 4 Therapeutic strategies for irritable throat syndrome.* Respiratory allergy screening may involve skin prick testing (with specific attention to aerosolised allergens) or radioallergosorbent test which identifies allergen-specific IgE in blood serum. ** A history of co-morbid psychiatric diagnoses should be taken. Screening tools which detect elevated levels of psychosomatic distress or identify elevated levels of anxiety or depressive symptoms may be useful adjuncts. *** 24-hour impedance pH manometry is the preferred assessment and aims to identify patients with high reflux burdens who may warrant consideration of ARS. ARS, anti-reflux surgery; GORD, gastro-oesophageal reflux disease; LPR, laryngopharyngeal reflux; CBT, cognitive behavioural therapy.



burden might initiate considerations for surgical intervention.

Specific treatment recommendations

Speech therapy as a core treatment: Speech therapists are pivotal in addressing diverse throat symptoms.^{10506795 110147}

Their treatment strategies may address sensory vigilance or hypersensitisation, motor tension and aberrant coordination and assist in disrupting self-sustaining phonotraumatic symptom cycles. All patients are recommended speech therapist-led treatment programmes to complement other therapeutic avenues.

Psychometric screening and behavioural interventions: The brain–gut connection in DGBI has highlighted the value of behavioural interventions for persistent non-structural symptoms, including throat symptoms.^{63 110 117 142 148–151} Psychological and behavioural interventions in the management of irritable throat symptoms therefore warrants further consideration.

Empirical PPI therapy: Sufficient data now establishes the limited efficacy of this option for isolated throat symptoms.^{35 38 152 153} We suggest that PPI is used principally when oesophageal symptoms of GORD are present.

Invasive reflux assessments: The value of invasive reflux assessments for guiding treatment and predicting response to reflux therapies for throat symptoms appears limited.^{28 33 34 154} Therefore, we recommend invasive reflux assessments only in patients with refractory symptoms, where surgical intervention might be warranted should a high reflux burden be detected.

Allergy screening and treatment The concept of AL is emerging and complements the proposed links between lower and nasal airway allergy and chronic throat symptoms. We suggest straightforward respiratory allergen sensitisation screening (ie, RAST panel) where allergy status is uncertain. A positive result may warrant trial of low-risk allergy therapies until evidence-based recommendations can be made.

Neuromodulators: Growing literature suggests moderate symptom benefits in patients with cough, dysphonia, globus and throat clearing when treated with neuromodulating agents. Given potential side effects, we suggest their empirical trial should be reserved for patients for whom first-line treatments have failed, and inflammatory contributions have been addressed or excluded, where applicable.

Limitations and future of therapeutic strategies

At present, the therapeutic landscape for irritable throat symptoms is inadequately explored, particularly with respect to biopsychosocial models. An interdisciplinary approach for irritable throat seeks to promote common perspectives and terminologies that enhance research data. We anticipate that these strategies, presented here as a starting point, will evolve considerably, benefiting from expanded options and evidence-based refinements.

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