Journal of Community Hospital Internal Medicine Perspectives

Volume 14 | Issue 6 Article 12

2024

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Dawlat Khan
Internal Medicine University of South Dakota Sanford School of Medicine, Sioux Falls SD, USD, dawlat.khan@usd.edu

Hammad Chaudhry
Internal Medicine University of South Dakota Sanford School of Medicine, Sioux Falls SD, USD

Phool Iqbal
Internal Medicine, Metropolitan Hospital Center, New York, NY, Unted states

Dawood Shehzad
Internal Medicine University of South Dakota Sanford School of Medicine, Sioux Falls SD, USD

Muhammad Yasir
Internal Medicine, Hackensack Palisade medical center, New Jersey, USA

Recommended Citation

Khan, Dawlat; Chaudhry, Hammad; Iqbal, Phool; Shehzad, Dawood; Yasir, Muhammad; Khan, Wahab; Zia, Aiman; and Ahmed, Mamoon (2024) "Cough-hypersensitivity syndrome-A new paradigm in the evaluation of chronic refractory cough and its novel therapeutic horizons-A Review," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 14: Iss. 6, Article 12.
DOI: 10.55729/2000-9666.1417
Available at: https://scholarlycommons.gbmc.org/jchimp/vol14/iss6/12

Cough-hypersensitivity syndrome-A new paradigm in the evaluation of chronic refractory cough and its novel therapeutic horizons-A Review

Authors

Dawlat Khan, Hammad Chaudhry, Phool Iqbal, Dawood Shehzad, Muhammad Yasir, Wahab Khan, Aiman Zia, and Mamoon Ahmed

Cough-hypersensitivity Syndrome-A New Paradigm in the Evaluation of Chronic Refractory Cough and Its Novel Therapeutic Horizons-A Review

Dawlat Khan [a,*], Hammad Chaudhry [a], Phool Iqbal [b], Dawood Shehzad [a], Muhammad Yasir [c], Wahab Khan [a], Aiman Zia [a], Mamoon Ahmed [a]

[a] Internal Medicine University of South Dakota Sanford School of Medicine, Sioux Falls, SD, United States
[b] Internal Medicine, Metropolitan Hospital Center, New York, NY, United States
[c] Internal Medicine, Hackensack Palisade Medical Center, New Jersey, United States

Abstract

Chronic cough is defined as a persistent cough, lasting beyond 8 weeks, poses a global health challenge, impacting a substantial portion of the world's population. In the United States, it stands as a prominent cause for numerous visits to primary care and pulmonology clinics, imposing a significant healthcare burden and utilizing valuable resources. While chronic cough can be indicative of serious underlying lung conditions, once serious pulmonary diseases are excluded, the leading culprits are often identified as gastroesophageal reflux, upper airway cough syndrome, and eosinophilic airway inflammation. Cough Hypersensitivity Syndrome (CHS) serves as a paradigm for understanding chronic refractory cough. CHS is chronic cough triggered by low-level tussigneic stimuli once more common etiologies have been effectively addressed. This review delves into the definition, pathophysiology, current therapeutic options, and novel treatments for Cough Hypersensitivity Syndrome (CHS).

Keywords: Cough hypersensitivity syndrome, CHS, Chronic refractory cough, CRC

1. Introduction

The precise global prevalence of chronic cough remains uncertain; however, it affects approximately 12% of the global population.[1] Regional and gender disparities are evident, with lower prevalence observed in Asia and Africa compared to Europe and North America,[2] and a higher incidence in women relative to men.[3] Notably, chronic cough stands as one of the most common causes of stress urinary incontinence in women.[4] Furthermore, smokers exhibit a greater susceptibility compared to non-smokers.[2] (see Table 1)

Chronic cough constitutes a significant burden on healthcare, accounting for 10–38% of respiratory-related healthcare visits in the United States and contributing substantially to healthcare costs.[5] Beyond the cough itself, associated symptoms such as vomiting, rib discomfort, syncope, impaired speech, and fatigue negatively impact the quality of life.[6] Individuals experiencing chronic cough also face a higher incidence of depression, contributing to reduced productivity and an overall diminished quality of life. Recognition of these associated symptoms and effective management strategies are essential for improving overall outcomes.[7]

Hence, in this review our primary emphasis will be on Cough Hypersensitivity Syndrome (CHS), a distinctive aspect within the realm of Chronic Refractory Cough (CRC). The scope of our review will encompass the etiologies, pathophysiology, clinical features, and emerging therapeutic strategies of CHS.

2. Cough hypersensitivity syndrome as a paradigm for insight into refractory chronic cough

Chronic Refractory Cough (CRC) represents a distinct clinical entity characterized by persistent

Received 30 April 2024; revised 27 August 2024; accepted 11 September 2024.
Available online 2 November 2024

* Corresponding author at: Internal Medicine University of South Dakota Sanford School of Medicine, 1400 West 22nd Street, Sioux Falls, SD, 57105, United States.
E-mail address: Dawlat.khan@usd.edu (D. Khan).

https://doi.org/10.55729/2000-9666.1417

Table 1. Cough Hypersensitivity Syndrome symptoms [38].

	Urge to cough	Allotussia	Hypertussia
Definition	irritation/itch/scratchy throat	cough triggered by non-cough stimulant	Enhanced sensitivity to cough- stimulants
Examples	Tickle Globus sensation "Foreign-body throat sensation"	Talking, Laughing Singing, Changing positions Humidity changes, Eating	Cold air, dry air Fumes, odor Dust, aerosols

cough, even when potential underlying factors such as asthma, acid reflux, and ACE therapy have been effectively addressed.[8] American College of Chest Physician (ACCP) guidelines advocate for a thorough clinical evaluation and standardized therapeutic trials before categorizing a patient as having Chronic Refractory Cough (CRC).[9] (Fig. 1) There is a substantial influx of referrals to chest specialist clinics for Chronic Refractory Cough or Unexplained Chronic Cough (UCC), with treatment failures ranging from 12% to 46%.[10] In 2014, the European Respiratory Society (ERS) Task Force introduced the concept of Cough Hypersensitivity Syndrome (CHS) to enhance clarity in defining chronic refractory cough. CHS is delineated as a clinical syndrome characterized by bothersome coughing, often triggered by low levels of thermal, mechanical, or chemical exposure.[11] ACCP guidelines advocate for the use of CHS, discouraging alternative terms such as habit cough or psychogenic cough.[12]

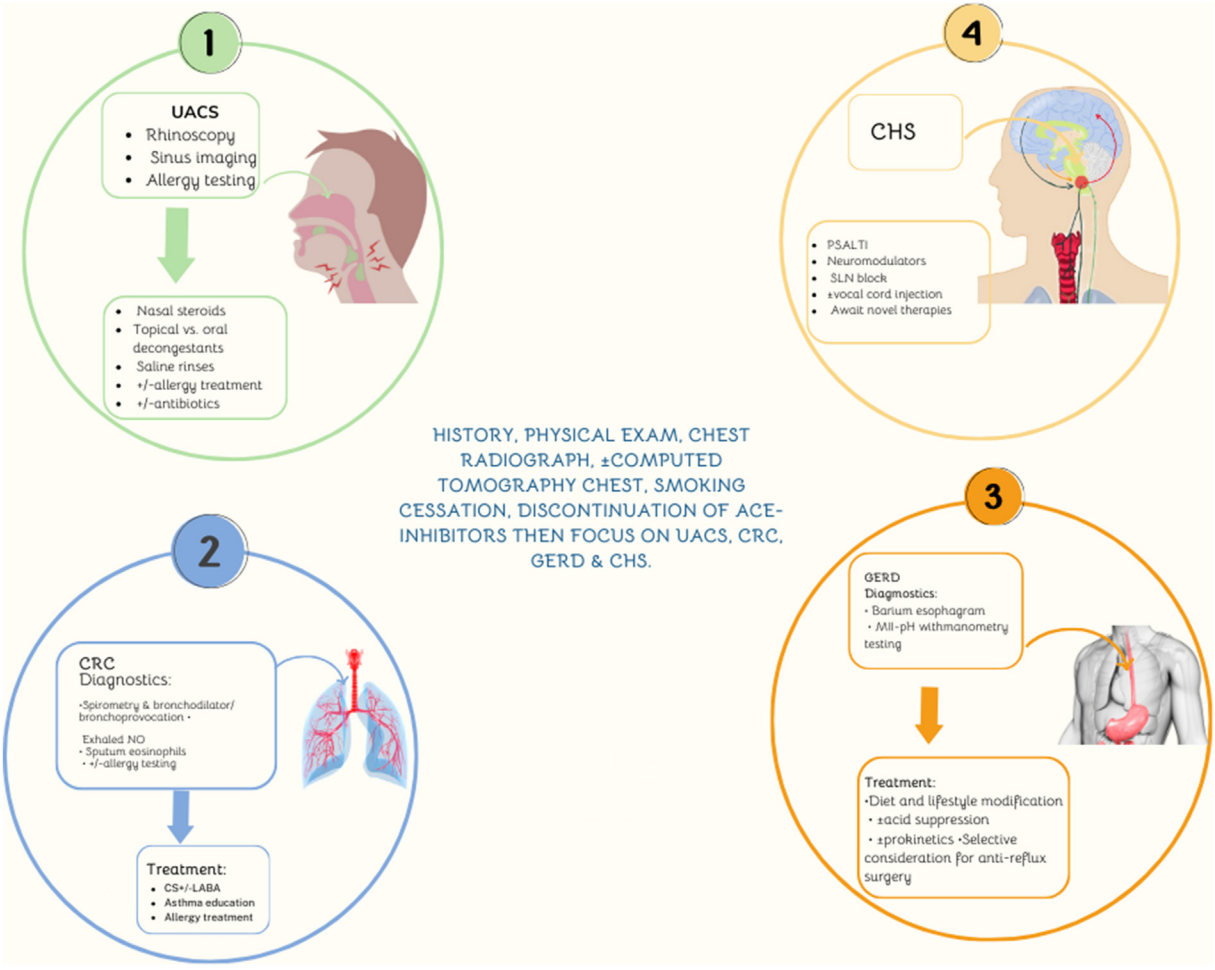

Fig. 1. American college of Chest Physician algorithm for chronic cough evaluation.1-Upper airway cough syndrome (UACS), 2-Corticosteroids responsive cough (CRC), NO-Nitric oxide. LABA: long-acting beta agonist. 3-Gastroesophageal reflex disease (GERD), 4-CHS-cough hypersensitivity syndrome. (PSALTI): Physiotherapy and Speech and Language Therapy Intervention. SNL-superior laryngeal nerve.

3. Distinguishing clinical features in support of CHS diagnosis

The primary manifestations of Chronic Hypersensitivity Syndrome (CHS) encompass symptoms related to laryngeal paraesthesia and an intensified perception of the urge to cough (UTC), described by patients as intermittent sensations of itch, tickle, scratch, irritation, choking, or Globus Pharynges (a sensation of lump or fullness in the throat). Additionally, symptoms may encompass chest tightness, dysphonia, voice hoarseness, and vocal cord dysfunction.[13]

CHS presents three frequently observed phenomena: Allotussia, hypertussia, and hypersensitive cough reflux.[14] Allotussia refers to coughing triggered by non-tussive stimuli, such as speaking, laughing, singing, deep inspiration, changes in body posture, fluctuations in air temperature/humidity, or exposure to fragrances, chemical scents, or specific food types. Conversely, hypertussia involves increased sensitivity to cough-inducing stimuli like capsaicin, citric acid, aerosols, fumes, or dust.[15] Notably, cough hypersensitivity refers to stimuli typically non-cough-inducing in normal individuals can induce coughing in CHS patients.[16] Although these phenomenon are frequently reported by patients but Unfortunately lack specificity for diagnosis of CHS.

4. Current pathophysiological understanding of cough hypersensitivity syndrome (CHS)

The intricate protective mechanism of cough involves a complex cough reflex arch, comprised of following components[17]: (Fig. 2).

1. Chemical and Mechanical Receptors: Found in the respiratory mucosa and nearby organs (ear canal, paranasal sinuses, pharynx, diaphragm, pleura, pericardium, and stomach).
2. Afferent Pathway: Mainly composed of unmyelinated C-Fibers traversing through the vagus nerve to central cough centres, Substance-P,

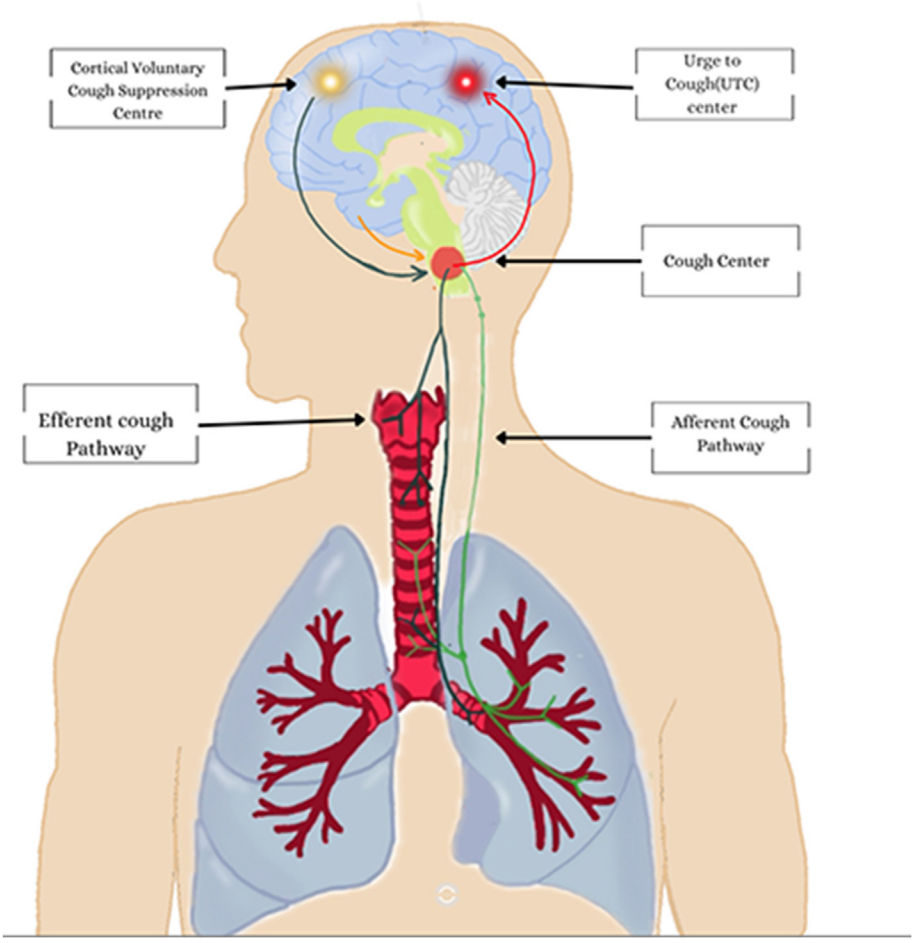

Fig. 2. Cough is a reflex arc.

neurokinins, and calcitonin gene-related peptides act as neurotransmitters.
3. Cetral Cough Centre (Central Pathway): Located in the upper brain stem and pons.
4. Efferent Pathways: Transmit impulses through the vagus, phrenic, and spinal motor nerves to the larynx, diaphragm, abdominal wall, and muscles.
5. Cortical Voluntary Cough Suppression Centre-mediate voluntary cough suppression
6. Urge to Cough (UTC): impulse for UTC are processed through a separate central pathway in the sensory cortex.[16]

The proposed pathophysiological mechanisms of Chronic Hypersensitivity Syndrome (CHS) involve maladaptation in both peripheral and central pathways. Chronic exposure to cough-triggering stimuli induces functional and phenotypic changes in the peripheral neuronal pathway, leading to cough hypersensitivity. These changes are primarily mediated by chemical and physical irritant-stimulated transient receptor potential channels, specifically vanilloid-1 (TRPV1) and ankyrin-1 (TRPA1), as well as P2X3 and tachykinin receptors.[18,19] This hypothesis is supported by the up-regulation of these receptors in viral infections and inflammatory airways diseases, correlating with heightened cough reflex sensitivity in these conditions.[20]

Although peripheral nerve hypersensitivity is a primary trigger, the down regulation of activity in central cough suppression centres equally contributes to the mechanism of CHS.[18] Functional brain MRI confirms neuronal hypoactivity in cough suppression brain areas, with corresponding volume reduction among patients with CHS compared to normal individuals.[21] Interestingly, this suppression pattern resembles that observed in chronic pain patients, suggesting a resemblance of central pathway processing of chronic pain and chronic cough.[8]

Capsaicin, present in hot chili peppers, strongly activates most of the TRPV-1 receptor family. The cough challenge test using capsaicin can assess the extent of both peripheral and central cough hypersensitivity, although its clinical significance is still under evaluation.[22] The Arnold nerve reflex can clinically assess vagal nerve hypersensitivity.[23]

5. Current therapeutics modalities

Chronic cough significantly affects both the physical and psychological aspects of a patient's quality of life, prompting the adoption of a multimodal management strategy. The following therapeutic modalities of Chronic Hypersensitivity Syndrome have been employed:

1. **Neuromodulators:** Given the recognition of cough reflux hypersensitivity as a key underlying pathophysiological mechanism in Chronic Hypersensitivity Syndrome (CHS), neuromodulators such as amitriptyline,[24] gabapentin25, baclofen,[26] and pregabalin27 have exhibited promising responses in reducing cough severity. However, their use is constrained by a broad range of associated side effects, limiting applicability to specific patient populations (elderly).[27]
2. **Speech Therapy Intervention:** Randomized clinical trials (RCTs) have established the significance of Speech Therapy in managing CHS. A specific therapeutic approach, known as Physiotherapy and Speech and Language Therapy Intervention (PSALTI), has been integrated into clinical practice and demonstrated a 41% reduction in cough frequency.[28] This comprehensive intervention includes psycho-educational techniques, voluntary cough control, and laryngeal hygiene.[6] Remarkably, the combined use of PSALTI and pregabalin has shown superiority over individual treatment modalities.[29]
3. **Direct Vocal Cord Therapies:** In cases where neuromodulation and PSALTI prove ineffective, direct vocal cord therapies, including botulinum toxin type A injections, vocal fold augmentation (methylcellulose and hyaluronic acid injections), and recently, superior laryngeal nerve blocks, are explored. However, these interventions come with associated side effects such as dysphonia and liquid dysphagia. These interventions are supported by small studies, and lack of randomized controlled trial (RCT) data, therefore typically employed in higher interventional research centres only.
4. **Tramadol**: 50 mg three times a day improved CSI (cough severity index) but carries a high risk for serotonin syndrome and chemical dependence (prospective case series).[30]
5. **Azithromycin:** (500 mg for 3 days, then 250 mg, three times a week) in double-blind randomized control trial only improve cough in patients with underlying asthma at the cost of GI side effects.[31]
6. **Non-pharmacological strategies:** The role of non-pharmacological management strategies, such as hypnosis and psychiatric or psychological referral, is also considered a contemporary approach, albeit further studies are warranted in

this domain.[32] Overall, the implementation of a multidisciplinary approach yields the most favourable outcomes for CHS management.

6. Innovative therapeutic approaches for cough hypersensitivity syndrome (CHS)

The utilization of neuromodulators has demonstrated promising outcomes in managing Cough Hypersensitivity Syndrome (CHS); however, their use has been constrained by the widespread adverse side effects. This limitation arises due to the predominant action of available neuromodulators on the central pathways of CHS. Over the past decade, significant efforts and resources have been dedicated to developing new drugs that target specific receptors within the peripheral neuronal pathway of CHS, aiming to minimize side effects. So far the following clinical trials have been conducted (Fig. 3).

1. **TRPV1 Receptors antagonist:** TRPV1 receptors that are stimulated by capsaicin, cold air, and air pollutants (e.g., smoking), were of primal interest. Two TRPV1 antagonists, SB-705498 and XEN-D0501, exhibited a reduction in capsaicin-induced cough reflux; however, they failed to decrease cough frequency or improve cough-specific quality of life (QoL).[33,34]
2. Gefapixant (AF-219): As a P2X3 receptor antagonist, Gefapixant displayed noteworthy outcomes in clinical trials, achieving a 75% reduction in cough frequency. The only limiting adverse effect was dose-dependent taste disturbance. Subsequently, three consecutive clinical trials were conducted with different doses:
   - Gefapixant 600 mg daily dose (2015, UK) showed dose-dependent taste disturbance.[35]
   - Gefapixant 100 mg daily dose (2019, UK) also exhibited dose-dependent taste disturbance.[19]
   - A Randomized Controlled Trial (RCT) in 2020 in the UK included four dosage groups:[36]
     - Placebo group
     - Gefapixant 7.5 mg daily group
     - Gefapixant 20 mg daily group
     - Gefapixant 50 mg daily group.

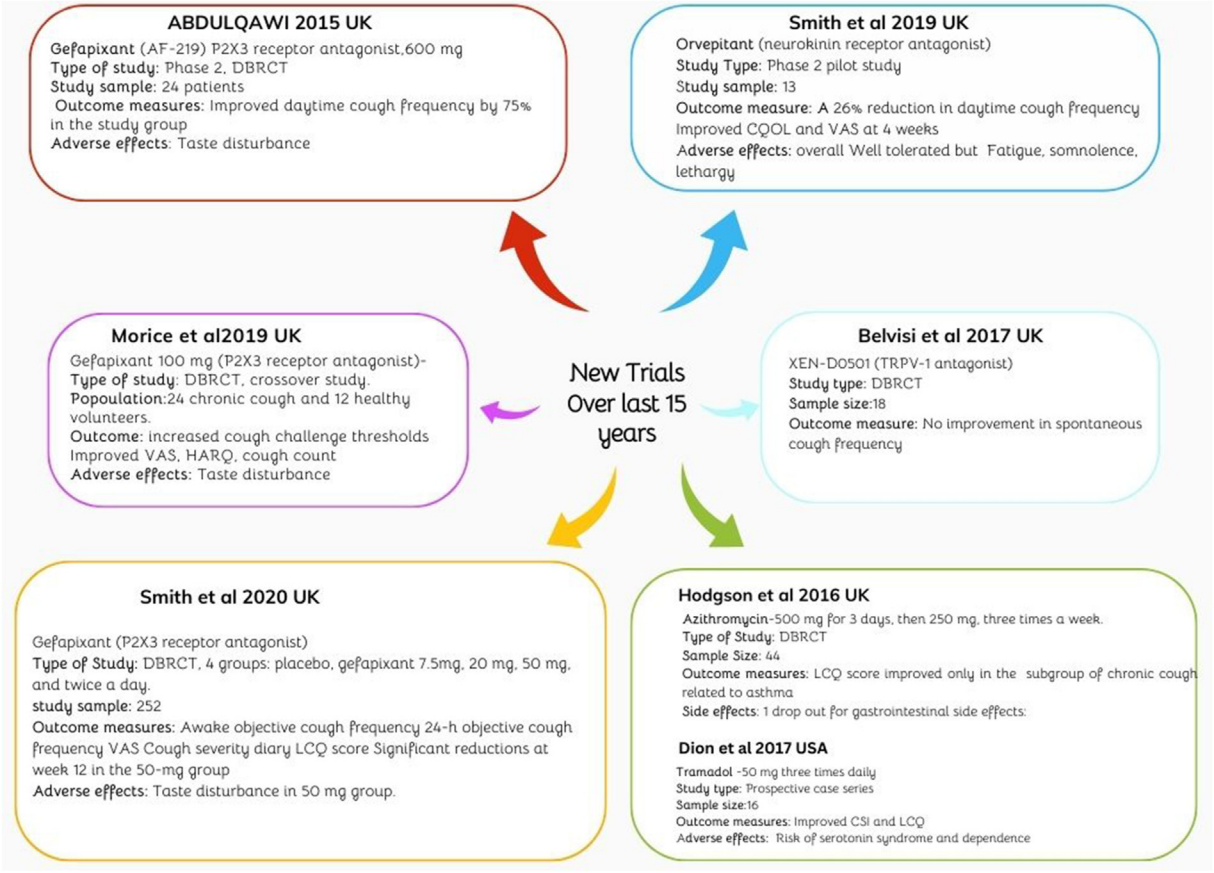

Fig. 3. Cough Hypersensitivity Syndrome (CHS) Randomized clinical Trials over the last 15 years.

Interestingly in this trial only a daily dose of 50 mg and more had taste disturbance.

3. Orvepitant: As a neurokinin receptor antagonist in a Phase-2 pilot study, Orvepitant alleviated daily cough by 26% compared to the placebo. Notable adverse effects included light-headedness, tiredness, and somnolence.[37]

7. Conclusion

Diagnosing chronic refractory cough (CRC) poses a considerable challenge both for clinician and patients, necessitating adherence to the algorithmic approach outlined in the ACCP guidelines prior to reaching a CRC diagnosis. Given the potential coexistence of multiple etiologies, the adoption of a multi-modal diagnostic and therapeutic strategy is crucial for optimizing outcomes. The emergence of Cough Hypersensitivity Syndrome (CHS) as a new paradigm offers valuable insights into the CRC. When CHS is the most likely diagnosis, a multidisciplinary approach, inclusive of Speech Therapy assessment, yields the most favorable outcomes. Healthcare professionals must stay vigilant regarding emerging therapeutic approaches and their potential approval by the FDA.

Funding

No funding was obtained for this project.

Conflict of interest

All authors declare no conflicts of interest, financial or otherwise, related to this publication.

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