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About the Author

Imran Satia, MA, MB BChir (cantab), PhD, MRCP

Dr. Imran Satia is a respirologist and associate professor at McMaster University and hold the Canada Research Chair in chronic cough. He is respiratory clinician-scientist with expertise in chronic cough. Imran completed a Masters in neurophysiology and medical degree at the University of Cambridge and subsequently completed clinical rotations in respiratory medicine and general internal medicine. Imran completed a PhD in the neuronal mechanisms of cough and was awarded the British Medical Association James Trust Award. He was awarded the European Respiratory Society Marie-Curie Global Fellowship, the E.J. Moran Campbell Early Career Award, and the ERS Mid-Career Gold Medal Award. Imran has also developed the McMaster Cough Severity Questionnaire for use in clinical trials.

Affiliations: Department of Medicine, McMaster University, Hamilton, Ontario, Canada
Firestone Institute for Respiratory Health, St. Joseph's Healthcare, Hamilton, Ontario, Canada

Management of Refractory Chronic Cough and Emerging Therapies in 2025

Imran Satia, MA, MB BChir (cantab), PhD, MRCP

What is Chronic Cough?

Chronic cough, defined as cough lasting for more than 8 weeks, affects approximately 10% of adults globally, with prevalence reaching as high as 16% in Canada.[1,2] Cough is the leading cause of ambulatory and primary care visits and one of the most common reasons for referral to secondary care.[3] Patients with chronic cough experience a median of 500 coughs per day, which significantly impairs their quality of life.[4] This high frequency of coughing leads to distressing physical, psychological, and social consequences, such as urinary incontinence, exhaustion, sleep disturbances, fatigue, anxiety, frustration, embarrassment, and social isolation, especially in the post-COVID era.

What is Refractory or Unexplained Chronic Cough?

Although most cases of chronic cough are benign, a careful approach is important to exclude serious underlying diseases such as lung cancer, tuberculosis, heart failure, and interstitial lung diseases. Clinical guidelines and statements from the European Respiratory Society (ERS) and British Thoracic Society emphasize the importance of a systematic evaluation and management algorithm for chronic cough.[5,6] Typically, when an underlying cause of chronic cough is identified and appropriately managed, and the cough improves sufficiently, it is considered resolved. However, when the chronic cough persists despite optimal treatment of identified conditions, it is termed refractory chronic cough (RCC). Cough that persists after a comprehensive investigation and lacks an identifiable cause is

termed unexplained chronic cough (UCC). While 'unexplained' chronic cough is commonly used in clinical trials for stratification of patients, it is seldom applied in clinical practice. This is because it may be perceived as dismissive to patients, as they may feel it invalidates their disease and may imply that there is no underlying pathology.

What is the Underlying Pathology of Refractory Chronic Cough?

Both RCC and UCC are also categorized as cough hypersensitivity syndrome. Coughing is an airway neuronal defensive reflex that acts to protect the airways from thermal, mechanical, and chemical damage.[7] Patients in clinical practice describe coughing being triggered by talking, laughing, singing, or being exposed to changes in temperature, strong smells, and chemicals in aerosols.[8] Human studies have identified that the vagus nerves innervate the airways and when stimulated, transmit action potentials to the central nervous system to initiate coughing. Clinical studies using cough stimulation (e.g., capsaicin) demonstrate that patients with RCC/UCC have an exaggerated and heightened cough reflex.[9] These findings suggest an underlying dysregulated neuronal reflex but it is unclear exactly where this neuronal hypersensitivity and hyper-responsiveness exists in an individual patient–it could be due to peripheral sensitization, central sensitization and/or impaired descending inhibitory control mechanisms.[7] These mechanisms also exist in chronic pain.

How to Take a Cough History?

A thorough history is the cornerstone of evaluating chronic cough.[10] Key features to assess include the duration and time course of the cough, any precipitating event, such as a viral infection, and its current frequency and severity, which can be quantified on a 0–10 numerical rating scale. It is also useful to characterize the nature of the cough (dry or productive, and if productive, the quantity and character of the sputum). The presence of triggers that reliably induce cough should be explored–many patients report cough triggered by cold air, strong smells, talking, or laughing, which is suggestive of a heightened cough reflex sensitivity. The history should also seek associated symptoms that might point to common cough aetiologies. For instance, ask about:

- **Asthma:** Look for nocturnal symptoms, wheeze, dyspnea, cough induced by cold/exercise.
- **Upper airway cough syndrome (UACS):** Ask about nasal congestion, rhinorrhea, or sinus pressure.
- **Gastroesophageal reflux disease (GERD):** Ask about heartburn, regurgitation, coughing after meals or when supine.
- **Medications:** Review use of ACE inhibitors, and less commonly, beta-blockers.
- **Red flags:** Be alert for hemoptysis, weight loss, fever, or night sweats.

It is also valuable to assess how the chronic cough affects the patient's quality of life, including its impact on their physical and psychological health, social interactions, work, and family life. Enquiring and documenting this impact helps to validate the lived experiences of patients.

What Investigations Should I Request?

The investigation of chronic cough should begin with a focused history and physical examination, followed by baseline tests recommended for all patients. A chest radiograph (CXR) is essential to rule out serious pathologies such as lung cancer, tuberculosis, or interstitial lung disease. While most CXRs will appear normal, any abnormalities or ongoing clinical suspicion, particularly in the presence of red flags such as hemoptysis, systemic symptoms, or smoking history, may warrant further imaging with a high-resolution CT scan.

Spirometry, ideally combined with bronchodilator testing, should be performed in all patients to assess for asthma or chronic obstructive pulmonary disease (COPD). If spirometry findings are normal but clinical suspicion for asthma remains, a bronchoprovocation test, such as the methacholine challenge, can confirm airway hyper-responsiveness. A positive response (e.g., 20% drop in forced expiratory volume in 1 second (FEV_1) at a provocative dose 20% (PD20) <400 mcg) supports a diagnosis of asthma. Additionally, induced sputum analysis may help identify eosinophilic inflammation (>2–3% eosinophils), confirming non-asthmatic eosinophilic bronchitis (NAEB), while the presence of neutrophilia may suggest infection.

Fractional exhaled nitric oxide (FeNO) is a non-invasive marker used to detect eosinophilic inflammation. Although current guidelines do not recommend its routine use due to variability in predictive values, a FeNO level >25 parts per billion (ppb) may suggest steroid responsiveness.[11] Some studies show that up to two-thirds of patients with elevated FeNO levels may improve with inhaled corticosteroids (ICS), with levels >50 ppb more strongly associated with eosinophilic airway disease.

In selected cases, bronchoscopy may be indicated if patients present with hemoptysis, abnormal imaging findings, suspected tracheobronchomalacia, or those who are immunocompromised, to identify infections. Referral to the Ear, Nose, and Throat team for nasolaryngoscopy is appropriate when there is suspicion of vocal cord dysfunction, muscle tension dysphonia, or other upper airway pathologies. For patients with persistent reflux-related cough that is unresponsive to proton pump inhibitors, or when esophageal dysmotility disorders are suspected, further testing with 24-hour pH-impedance and esophageal manometry monitoring may be considered.

What Treatments Should I Consider?

Management of chronic cough starts with treating any identifiable underlying disease or treatable trait. In many patients, cough can be due to one or more common conditions such as asthma, NAEB, UACS, or GERD. When clinical evaluation and investigation suggests a specific etiology or trait, a focused trial of therapy is appropriate, as shown below (see **Figure 1)**.

- **Asthma and Eosinophilic Bronchitis:** ICS are first-line therapy for asthma-related cough. A 6–8 week trial can assess efficacy, with bronchodilators or leukotriene receptor antagonists added as needed. In cases of NAEB, initial therapy may include a medium-to-high dose ICS or a short oral steroid course. However, ICS should not be prescribed without evidence of eosinophilic inflammation, as they are unlikely to be beneficial otherwise.
- **Upper Airway Cough Syndrome:** UACS includes cough associated with rhinitis or sinusitis. Empirical treatment typically includes intranasal corticosteroids and/or first-generation antihistamines. For patients with allergic rhinitis, second-generation antihistamines or leukotriene antagonists may help. Additional symptom relief can be achieved with nasal saline irrigation and short-term decongestants. In cases of vasomotor rhinitis, intranasal anticholinergic agents may offer therapeutic benefit.
- **Gastroesophageal Reflux Disease/Esophageal Dysmotility:** Lifestyle measures—such as avoiding late meals, caffeine, and acidic foods—are essential. In patients with typical reflux symptoms, a trial of twice-daily proton pump inhibitors for 8 weeks is reasonable, though efficacy is limited in cases of silent reflux. If symptoms do not improve, proton pump inhibitors should be discontinued. Further interventions such as H_2 blockers or surgery are rarely needed when cough is the sole symptom. For patients with confirmed esophageal dysmotility, low-dose macrolides or prokinetics such as domperidone or metoclopramide may be considered, but should be used with caution due to potential side effects. Referral to gastroenterology is advised following pH-impedance and manometry testing.
- **Chronic Bronchitis (COPD):** For patients who smoke and have a chronic productive cough, address smoking cessation and optimize COPD management. Inhaled long-acting muscarinic antagonists may reduce cough. In selected patients with neutrophilic bronchitis, low-dose macrolide antibiotics may be used to prevent exacerbations; however, they are not routinely recommended solely for cough.
- **ACE Inhibitor-Induced Cough:** When an ACE inhibitor is identified as the cause, discontinuing the medication usually results in symptom resolution within a few weeks to months. Substituting with an angiotensin receptor blocker is effective and well-tolerated.
- **Obstructive Sleep Apnea Syndrome:** Weight reduction and treatment with continuous airway pressure (CPAP) can improve cough and overall quality of life.

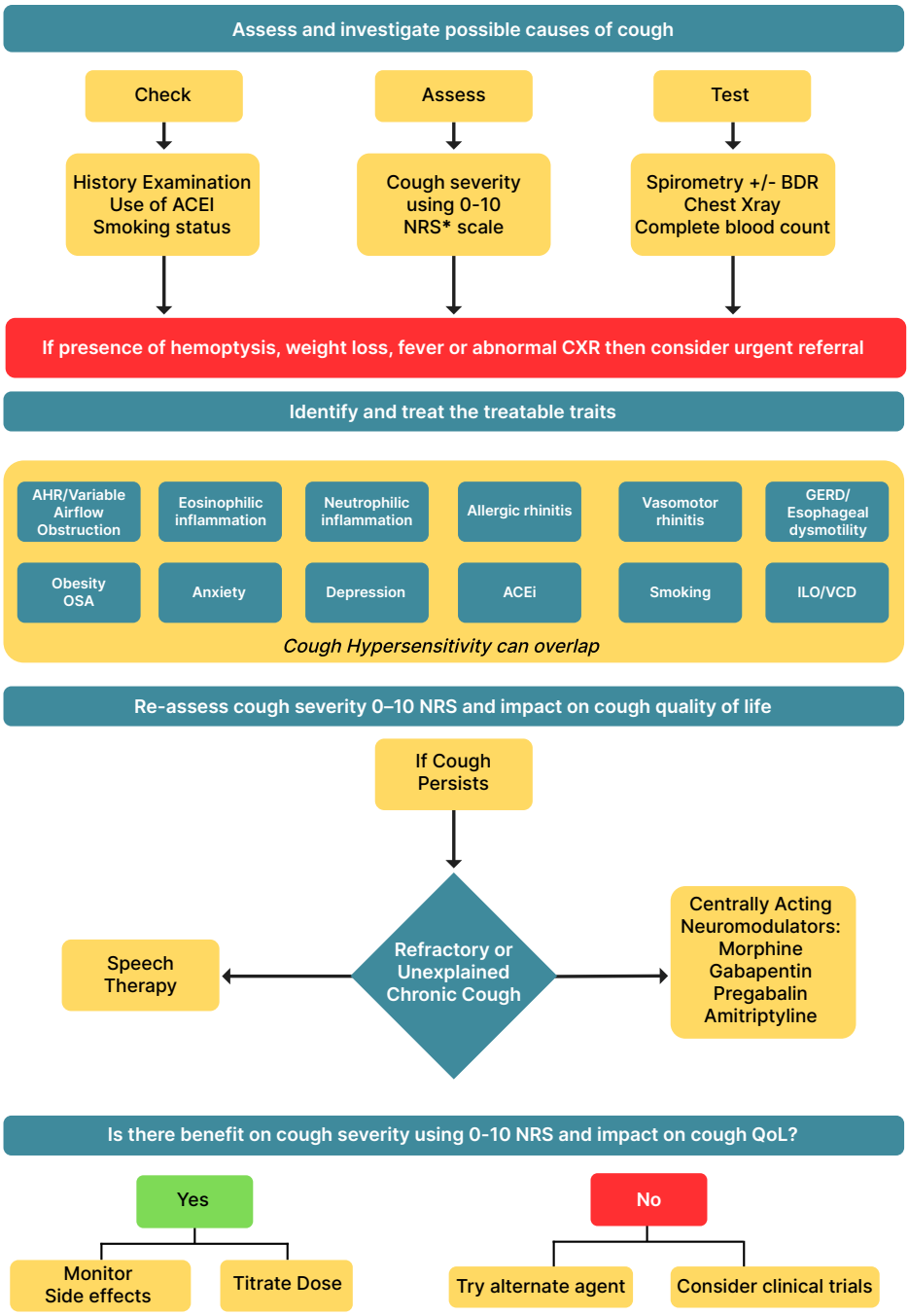

Figure 1. A clinical approach to the investigation and management of chronic cough. This algorithm guides clinicians through a series of steps, starting with an assessment of the patient's history and physical examination, followed by targeted diagnostic tests to identify treatable traits and potentially overlapping cough hypersensitivity early in the process. It emphasizes the importance of regularly assessing cough severity and its impact on quality of life, helping to determine whether a patient may have an RCC; *courtesy of Basmah Boblai.*

***NRS:** numeric rating scale.

Abbreviations: ACEi: angiotensin converting enzyme inhibitors, **AHR:** airway hyper-responsivness, **BDR:** bronchodilator response, **GERD:** gastroesophageal reflux disease, **ILO:** Inducible laryngeal obstruction, **NRS:** numeric rating scale, **QoL:** quality of life, **OSA:** obstructive sleep apnea, **RCC:** reactive chronic cough, **VCD:** vocal cord dysfunction.

- **Mental Health Disorders:** Anxiety and depression are common in patients with RCC and are considered independent risk factors. Hence, these conditions should be evaluated and considered for treatment. The use of amitriptyline in these patients may provide dual benefits.
- **Vocal Cord Dysfunction or Inducible Laryngeal Obstruction:** Vocal cord dysfunction (VCD)/ Inducible laryngeal obstruction (ILO) often coexist with chronic cough and laryngeal hypersensitivity, and should be considered particularly when cough is triggered by talking, laughing, or strong smells, or when patients describe throat constriction, dysphonia, and acute breathlessness. Speech therapy, minimizing triggers, and addressing co-morbidities can be helpful.

Empiric treatment should be avoided in the absence of clinical or objective evidence. Patients should be encouraged to complete the appropriate duration of treatment. Intervention fidelity is important for identifying RCC and preventing future repeated trials of treatment.

Which Neuromodulators to Try?

In patients with RCC, who have not responded to conventional treatments, neuromodulators can be used to attenuate the heightened cough reflex. Although these agents are used off-label, they are recommended by guidelines and have demonstrated efficacy in small clinical trials, as described below.

- **Low-dose morphine** (5–10 mg twice daily) has shown the most consistent benefit, with approximately half of patients experiencing a meaningful reduction in cough frequency.[12] An initial 1–2 week trial is recommended, with careful monitoring for side effects such as constipation and drowsiness. If the treatment is tolerated and effective, it can be continued with periodic reassessment to avoid long-term dependence. Codeine may be considered when morphine is unavailable, though supporting evidence for its use is comparatively limited.
- **Gabapentin**, an anticonvulsant with neuromodulatory properties, has been shown in a randomized trial to improve cough-related quality of life and reduce cough frequency.[13] Doses are titrated slowly to mitigate side effects such as sedation and dizziness, with a typical target of 900–1800 mg/day. A two-month trial is appropriate, after which treatment can be tapered if found effective.
- **Pregabalin**, a compound related to gabapentin, may offer similar benefits and is especially useful when combined with speech therapy.[14] It is generally started at 50 mg twice daily with gradual increases in the dose. As with gabapentin, it requires careful monitoring for tolerability and effectiveness.
- **Low-dose amitriptyline** (10–25 mg at bedtime) may be considered when other agents are ineffective.[14] While supported mainly by low quality evidence, it may offer benefit to select patients, particularly those with overlapping features such as insomnia or mood symptoms.

Overall, neuromodulators provide a treatment option for RCC; however, successful use depends on patient selection, gradual dose titration, and monitoring for adverse effects.

When to Refer to Speech Therapy?

Speech and language therapy (SLT), also termed cough control therapy or physiotherapy for cough, is a non-pharmacological intervention for RCC. This approach involves referral to a speech-language pathologist or physiotherapist who is trained in cough control techniques. The therapy typically includes education about cough hypersensitivity, training in breathing exercises, vocal hygiene practices, and strategies to suppress the urge to cough, such as using swallow or breathing techniques instead of coughing. Guidelines endorse speech therapy as a safe and effective adjunct or alternative to pharmacological treatment in chronic cough management.[15] SLT can be especially valuable for patients who either prefer to avoid drug therapy or who have not tolerated or responded to neuromodulators. The main challenges are the availability of respiratory therapists or physiotherapists skilled in cough-specific speech therapy, and ensuring patient adherence

to exercises. When accessible, SLT can yield meaningful symptom improvement and empower patients with techniques to control their cough in day-to-day life.

What Are the Future Treatment Options?

After years of limited treatment choices, several novel therapies for chronic cough are now in development, primarily targeting peripheral sensory pathways involved in cough hypersensitivity. Among the most promising developments are P2X3 receptor antagonists, which work by blocking ATP-gated ion channels on vagal sensory neurons. Gefapixant, the first-in-class P2X3 antagonist, has shown modest efficacy in large phase 3 trials, reducing cough frequency by 15–18% compared to placebo.[16,17] However, regarding its tolerability, up to 67% of patients experienced taste disturbances, with 13% withdrawing from the study in the first month. Gefapixant is currently approved in regions including parts of Europe, the UK, and Japan, though it is not yet approved in the United States or Canada. Camlipixant, a second-generation P2X3 antagonist, demonstrated greater efficacy, achieving a 34% reduction in cough frequency and fewer taste-related side effects in a phase 2b study.[18,19] Ongoing phase 3 trials (CALM-1 and CALM-2) aim to confirm its long-term benefit and safety. Nalbuphine, an oral kappa-opioid receptor agonist and mu-antagonist, has also shown promising results in phase 2 trials, including among patients with idiopathic pulmonary fibrosis.[20] phase 3 studies are in progress to confirm these findings.

In contrast to the promising results observed with P2X3 receptor antagonists, clinical trials targeting other sensory pathways, such as TRPV1, TRPA1, and TRPV4 ion channels, have largely shown disappointing findings. While these receptors are involved in irritant detection, their antagonists have not demonstrated meaningful benefit in treating chronic cough. Research continues into newer compounds, including TRPM8 inhibitors and sodium channel blockers, which remain under investigation.

Collectively, these developments suggest that targeted, mechanism-based therapies may soon transform the management of RCC.

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Correspondence

Imran Satia, MA, MB BChir, PhD, MRCP
Email: satiai@mcmaster.ca

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