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Chronic Cough, a New Disease, Not Just An Old Problem

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Definition

Chronic cough is defined as a cough persisting for longer than 8 weeks.[1] Chronic cough is common, with an approximate prevalence of 10% of the global population.[2] In Canada, recent estimates indicate that the prevalence of cough is 16% among adults aged 45-85 years.[3] Chronic cough can interrupt work, sleep, and social interactions, making it very troubling for patients, with impacts on physical, social, and psychological health.[4]

Cough is one of the leading causes of visits to primary care practitioners.[5] The peak incidence for presentation to primary care is among individuals in the 50-60 years age group and it is twice as frequent in women.[6]

Currently, most clinicians address cough as a symptom of other medical conditions, which leads to trials of treatments for diseases that may not be present. This approach can lead to unnecessary costs, frustration for both clinicians and patients, and potential harms from the therapies prescribed. Instead, a diagnostic work up needs to be performed to identify refractory chronic cough as a distinct disease entity, resulting from afferent neuronal hypersensitivity and central nervous system dysfunction.[7] The secondary factors that aggravate chronic cough (smoking, asthma, gastro-esophageal reflux, among others) should be considered as treatable traits associated with the primary disease process rather than only the direct causes of the cough.

Mechanisms of Cough

Cough begins as a normal protective physiologic process which helps with clearing of debris and secretions from the lungs and airways. It is important to understand that this is partly a neuronal process that involves 3 components: an afferent sensory limb, a central processing centre, and an efferent limb.[8] The afferent pathways contain cough receptors supplied by the trigeminal, glossopharyngeal, and vagus nerves. The vagus nerve supplies most of these receptors through the pharyngeal, superior laryngeal, and pulmonary branches. Cough receptors are distributed from the proximal airway in the pharynx down to the distal bronchioles, however, the highest concentrations are present in the larynx, carina, and the bifurcation of larger

bronchi. The receptors respond to many different stimuli including mechanical stimuli, pulmonary congestion, atelectasis, bronchoconstriction, cigarette smoke, ammonia, acidic and alkaline solutions, hypotonic and hypertonic saline, histamine, bradykinin, prostaglandins, substance P, and capsaicin. Some of these stimuli are targets for treatments, while others are used in diagnostic testing to establish cough hypersensitivity.

The impulses from the afferent nerves are transmitted to the cough centre of the brain, which then stimulates the central respiratory generator. This reflex arc is completed when impulses are sent via the vagus nerve and to the phrenic and spinal motor nerves from C3 to S2, supplying the intercostals muscles, abdominal wall, diaphragm, and pelvic floor, all of which assist in generating the cough. Recognizing that all nerves have neuroplasticity potential allows us to understand that the cough induces chronic irritation and inflammation in the tissues and the nerves supplying them. This leads to remodelling, which causes the tissues and nerves to become sensitized.[9] This sensitization occurs both peripherally, by increasing the sensitivity of cough receptors, and centrally, by changing processing in the brainstem, leading to an exaggerated cough response. This process is similar to how readers understand the development of chronic neuropathic pain.

Chronic cough may result from respiratory diseases such as asthma and chronic obstructive pulmonary disease, or non-respiratory issues such as gastro-esophageal reflux disease (GERD) and upper-airway cough syndrome (UACS).[10] However, when cough persists despite treating these underlying diseases, it is termed refractory chronic cough (RCC). If no cause is identified, it is referred to as unexplained chronic cough (UCC).

Chronic cough causes great suffering for patients, including social isolation, embarrassment, dysphonia, and urinary incontinence.[11,12] A Canadian study[12] showed its significant effects on mood, work performance, and the costs associated with cough related medications.

Diagnostic Steps

RCC and UCC have also been described as hypersensitivity cough and should be considered as distinct clinical entities. To diagnose these conditions, other causes need to be considered and treated or ruled out. A multitude of things can cause chronic cough; thus, an organized approach is required.

In order to reach a diagnosis, clinicians should rule out other common and uncommon conditions. Beginning with the patient's history, clinicians should consider potentially associated conditions such as asthma, GERD and UACS, as well as occupational and smoking history. In addition, upper airway issues such as vocal cord dysfunction or esophageal dysmotility which may present with symptoms of dysphonia, choking, or swallowing difficulties should be considered. Patients with UACS may have a history of postnasal drip, sinusitis, rhinorrhea, and nasal congestion. Asthma may be indicated by a history of wheeze, dyspnea, allergies, nocturnal cough, or cough triggered by exercise or cold air. Chronic obstructive pulmonary disease may present with progressive breathlessness and cough in a setting of lung damage, most commonly caused by cigarette smoking in Canada, but also consider biomass and occupational exposures. Patients with GERD usually experience heartburn, dyspepsia, dysphonia, or hoarseness, which may occur after a meal, when lying down, or bending forward. Chronic productive cough may prompt consideration of bronchiectasis, chronic bronchitis, or non-asthmatic eosinophilic bronchitis (NAEB). When assessing patients at risk of tuberculosis, consider their geographic location and whether they have come from endemic areas. Pertussis needs to be considered, especially when vaccination is suboptimal. Keeping lung cancer in mind is important, and clinicians should note that many cases are not related to cigarette smoking **(Table 1)**.[13]

A medication history is important, as cough can be a side effect of many medications, most notably angiotensin-converting enzyme (ACE) inhibitors, among others. Immunosuppression is a risk for many infections, including some unusual ones. In addition, a history of COVID is now relevant, as cough has been reported as a post-COVID condition.[14] Interestingly, family history might be relevant, as there may be some genetic components in identifying types of chronic cough; however, this work is in its early stages.[15]
Often patients have undergone trials of therapy, to 'rule out' conditions. However, it is important to review the specifics of these therapies. Was the duration adequate? For example, proton pump Inhibitors (PPI) for GERD require several months to be effective, and inhaled corticosteroids require at least 6-8 weeks to show benefits. Addressing issues like actual adherence and proper inhaler

Questions to ask
1. Duration of cough
2. Is the cough productive
3. If productive, is it purulent
4. What medications is the patient currently taking
5. Has the patient travelled to, or originated from, a tuberculosis-endemic region
6. What therapy trials have been conducted, and were they adequate
7. Does the patient have heartburn, postnasal drip, or wheeze
8. What is the effect of the cough on the patient's life
9. Does the patient smoke or have any other significant exposures

Table 1. Considerations in the diagnosis of chronic cough; *courtesy of Alan Kaplan, MD, CCFP(EM), CPC(HC)*

Red flags for urgent assessment and consideration of referral
1. Hemoptysis
2. Weight loss
3. Fever and/or night sweats
4. Radiologic abnormalities
5. Dyspnea
6. Hoarseness
7. Trouble swallowing
8. Persistent abnormalities in the chest exam such as crepitations, or focal wheezing
9. Other concerns of lung cancer such as new cough, voice loss, and nonspecific symptoms

Table 2. Considerations for urgent assessment and/or referral of chronic cough; *courtesy of Alan Kaplan, MD, CCFP(EM), CPC(HC)*

technique requires some finesse.

Consider red flags such as hemoptysis, weight loss, and fever **(Table 2 and Figure 1)**, which may change the order and urgency of investigations and considerations. Nonetheless, with a normal chest x-ray, the most common causes of chronic cough remain UACS, asthma, eosinophilic bronchitis, GERD or importantly, some combination of these conditions.

The physical exam may be normal, and findings such as mucus in the hypopharynx or cobblestoning of the oropharyngeal mucosa, when present, are not specific for UACS. Often, patient's do not report postnasal drip.[10] Examining the nose, especially with a nasal speculum, can show turbinate congestion, septal deviation, or nasal polyps. Auscultation of the chest may show crepitations, wheezing or hyperinflation.

A chest radiograph (CXR) is the next step for virtually all patients with chronic cough. Surprisingly, it is often not performed.[16] Findings on the CXR can direct further testing such as a chest CT scan, bronchoscopy, needle biopsy, and sputum studies.

Spirometry, which measures airflow, is the gold standard for diagnosing chronic obstructive pulmonary disease with fixed airway obstruction and asthma with reversible airway obstruction. However, false positives can occur with some conditions such as bronchiectasis. False negatives can occur with normal spirometry as asthma is a variable disease. The Global initiative for Asthma recommendations (GINA) recommends considering bronchial challenge testing to diagnose cough variant asthma.[17] Restriction, not obstruction, is the hallmark of other underlying lung diseases such as interstitial pulmonary diseases.

Measuring biomarkers consistent with eosinophilic airway inflammation can help point to obstructive airways disease such as asthma, NAEB and even COPD with type 2 inflammation. While fractionated exhaled nitric oxide (FENO) is not widely available, it can be helpful. Additionally, a CBC to check the blood eosinophil count (BEC) can be helpful, especially when the BEC is ≥300.

It is quite common for patients who have been treated unsuccessfully for UACS, asthma, and NAEB, are not on an ACE-inhibitor, and have a normal CXR, to have chronic cough due to GERD.[18] Look for classic symptoms such as reflux, heartburn, as well as less classic signs such as dental erosions or voice changes. Silent GERD has often been postulated as a cause of chronic cough, but the literature suggests this is less likely. Referral for upper gastrointestinal endoscopy can be considered. The diagnosis of GERD is best made with 24-hour pH probe monitoring, but this is not a first-line investigation due to cost, availability, and discomfort. It should be considered for those who are refractory to therapy. For those with voice changes, flexible nasopharyngoscopy can reveal changes in the glottis that are known to occur with exposure to reflux, such as laryngeal edema and erythema, laryngeal pseudosulcus, and posterior commissure

Proposed Primary Care Approach to Assessing Adults with Chronic Cough

Primary Investigations

To aid in diagnosis and/or referral

- Consider duration of symptoms (chronic cough definition >8 weeks)
- Is the cough chronically productive?/purulent?
- Review Red Flags (see below)
- Review medical history, including potential triggers:
  - Smoking, ACE inhibitors, sitagliptin?
  - Occupational/environmental issues or travel exposure?
- Perform physical exam
- Complete chest radiograph

Red flags for more severe issues

- Hemoptysis
- Smoker >45 years with new cough, cough change or coexisting voice disturbance
- Age 55-80 years: 30 pack-year smoking history + current smoker or quit <15 years ago
- Prominent dyspnea, especially at rest or at night
- Hoarseness
- Systemic symptoms, including fever, weight loss, peripheral edema with weight gain
- Trouble swallowing while eating or drinking
- Vomiting
- Recurrent pneumonia
- Abnormal respiratory exam and/or chest radiograph coinciding with duration of cough

Cough persists

Work-up for Potential Underlying Conditions

(Reassess in 4-6 weeks at least)

Assess for and treat as needed (alone or in combination)

Asthma

- Testing: spirometry
- Exploratory initial treatment per guidelines if indicated

GERD

- Exploratory initial treatment per guidelines if indicated
- Consider initiating referral to secondary care while waiting for testing/treatment results
- Assess if treatment resolved chronic cough

Other potential causes of chronic cough (some assessed in secondary care) including

- UACS
- NAEB
- Bronchiectasis
- COPD/Chronic bronchitis
- Infections

Cough persists

While Patient Waits to be Seen by Specialist

To expedite future diagnosis

- Consider other potential causes/additional investigations
- Consider possibility of >1 cause
- Assess adherence to treatment of potential underlying conditions
- Re-evaluate patient for (subtle) symptoms
- Continue to support your patient through their journey

Additional investigations (depending on access to testing)

- 24-hour esophageal pH monitoring
- Endoscopic/videofluoroscopic swallow evaluation
- Barium esophagram/modified barium swallow
- Sinus imaging
- HRCT
- Bronchoscopy
- Cardiac workup (ECG, Holter monitoring, Echo)
- Environmental/occupational assessment
- Sputum cultures +/- AFB
- Airway provocational challenges
- Uncommon causes?

Figure 2. Proposed Primary Care Approach to Assessing Adults with Chronic Cough; *Adapted from 2018 ACCP Guidelines Irwin RS et al. Chest 2018;153(1):196-209.*

Abbreviations: ACE: angiotensin-converting enzyme; **ECG:** electrocardiogram; **HRCT:** high resolution computed tomography; **GERD:** gastro-esophageal reflux disease; **NAEB:** non-asthmatic eosinophilic bronchitis; **PNDS:** post-nasal drip syndrome; **UACS:** upper airway cough syndrome; **AFB:** acid fast bacilli.

hypertrophy.

Recurrent aspiration can only be diagnosed by a thorough history and either observing the patient drink water, or by involving a speech-language pathologist for assessment.

NAEB can be diagnosed with an induced sputum test showing airway eosinophilia, alongside normal airway function testing, bronchoscopy with lavage, and potentially biopsy. Clearly these are not primary care tests and as such need a referral. Clues to this condition include asthma-like features (family history, elevated biomarkers such as BEC or FENO), but with normal spirometry. Treatment includes inhaled corticosteroids, with oral corticosteroids often needed for refractory cases.

Many of these steps require referrals to specialists, such as allergists, respirologists, gastroenterologists, otolaryngologists, and cardiologists. While your initial thoughts are generally correct, if you are truly puzzled or the cough has been refractory for many years, the best option may be to make a referral to multiple specialists simultaneously, instead of the typical linear thinking process of trying a therapy, making a referral and then reassessing. While intellectually proper, these linear referrals may contribute to patient frustration with long delays in reaching a diagnosis.

Treatment of Common Conditions

Regardless of etiology, smoking cessation should be encouraged and assisted.

UACS can be both allergic and non-allergic and is usually associated with postnasal drip, the sensation of liquid dripping down the posterior nasopharynx. Treatments can include oral or nasal antihistamines, nasal corticosteroids, or ipratropium if rhinorrhea is predominant compared to congestion. Decongestants should be avoided.

The only effective treatment for an ACE-inhibitor-induced cough is discontinuing the ACE-inhibitor. Improvement can be seen within 4-8 weeks, although cases have been reported to take up to 6 months.[19]

Treatment for GERD includes non-pharmacologic treatments including elevating the head of the bed, avoiding heavy meals at night, and avoiding foods that lower the esophageal sphincter pressure such as caffeine, alcohol, smoking, citrus, and chocolate. If there is objective evidence of reflux or at least symptoms, a trial of a PPI at full doses for at least 8 weeks can be considered. Although promotility agents might seem like a good idea, there is no substantial evidence behind their use.

Eosinophilic airway diseases such as asthma and NAEB require 6-8 weeks of at least moderate strength inhaled steroids with appropriate inhaler technique. For those in whom adherence is likely an issue, a trial of oral steroids for 1-2 weeks can be considered,[20] but again concerns of systemic steroids should be evaluated and reviewed. If there is no evidence of eosinophilic airway disease, inhaled steroids are unlikely to be of benefit.[21] Leukotriene receptor antagonists have been shown to be effective as an adjunct to inhaled corticosteroids/long-acting beta-agonists in cough variant asthma in some small randomized controlled trials,[21,22] offering a potential treatment option. However, recent recognition of neuropsychiatric side effects warrants caution. There is no evidence that biologics specifically reduce chronic cough, though some have been shown to reduce mucus scores both clinically and radiologically.

Hypersensitivity Cough Syndrome

When all tests are normal or expected to be normal, recognition of hypersensitivity cough syndrome, which has many names, is needed for providing a diagnosis for both the patient and clinician. Understanding that this is a disease entity is important. Although there is no cure, there are treatments that can help. In addition, reassuring the patient that their condition is real can be immensely beneficial, especially for those who have been suffering for a long time.

Since current treatments often have a degree of 'trial and error' or 'n of 1' trials, it is of benefit to measure something objectively to assess treatment success. Studies have used devices to count coughs, and new applications on digital phones can help.[23] Further, capsaicin sensitivity tested in organized laboratories can safely help assess outcomes.[24] A simple tool is the Leicester Cough Questionnaire,[25] which consists of 19 questions. These scores are summed and divided by 19 to provide a summary of how well the patient is doing overall. This tool is akin to many of the patient-related outcome measures we use in primary care such as COPD Assessment Test (CAT), Asthma Control Questionnaire (ACQ), Brief Pain Inventory (BPI), Patient Health Questionnaire-9 (PhQ 9) and General Anxiety Disorder-7 (GAD 7). Objective measurements of

therapy trials can help clarify follow up decisions and should be used with the neuromodulator therapies mentioned below.

Where available, speech and language therapy is a safe and effective option for patients who desire non-pharmacologic therapy or who have had side effects from neuromodulators.[26] This therapy provides education, cough suppression exercises, cough avoidance strategies, strategies to reduce laryngeal irritation, and speech counselling and support. However, maintaining adherence to the necessary exercises can be an issue.

Neuromodulator treatment, similar to trials for neuropathic pain, includes low-dose morphine, gabapentin, pregabalin, and tricyclic antidepressants. These treatments have shown effectiveness in small studies but are associated with significant side effects such as dizziness, drowsiness, unsteadiness, and fatigue. The adage of 'start low, go slow' is appropriate here, with no large studies to provide dosing guidance. If there is no benefit, clinicians should discontinue the treatment.

Opioid therapy can be helpful and should be trialled for 1-2 weeks after discussing the pros and cons with the patient. Start with a low dose, usually 5-10 mg of slow or modified-release morphine twice daily, and review for efficacy, which is usually observed within 3-7 days. If the patient does not benefit from a 1-2-week trial, the opioids should be discontinued. This short duration is unlikely to lead to withdrawal symptoms. If there is benefit, the dose of the opioid can be titrated to minimize side effects such as constipation, drowsiness, and sedation. I would suggest to proactively manage constipation with laxatives or Naloxegol, a peripheral opioid receptor antagonist indicated for opioid induced constipation. Alternative opioid regimens include once daily dosing at night, alternate day dosing, or when required 3-4 hours before socializing, teaching, or attending important public events.[22]

An organized approach with opioids, as described above, is preferable to using narcotic-containing cough syrups for regular treatment. It is important to remember that opioid cough syrups also have a potential for misuse.

Experimental interventions have included superior laryngeal nerve blocks via injection of local anesthetic and corticosteroid injections, as well as vocal fold augmentation with methylcellulose or hyaluronic acid. However, the studies on these treatments are small and lack controls and require special expertise. Additional data is needed in my opinion, especially considering the reported side effects including brief laryngospasm, temporary throat paresthesia, and the risk of blindness or stroke due to embolization of particulate steroids into the arterial circulation.

Electromyography (EMG)-guided thyroarytenoid (TA) Botulinum Toxin A injections have demonstrated a self-reported improvement in cough of 50% or more after the first injection.[27] Adverse effects include temporary liquid dysphagia and dysphonia.

Several treatments are currently under investigation for treatment of RCC/UCC. They include blockers of both the peripheral and central nerves. Some have shown encouraging results, with novel oral P2X3 antagonists seemingly closest to market. However, further studies are needed.

Therapy trials with nebulized lidocaine may be effective for a small group of patients.[28] However, this therapy tends to lose effectiveness over time and is associated with side effects including throat numbness, dysphonia, and swallowing issues.

In patients with chronic cough from pulmonary fibrosis (but not RCC), some studies have shown success. High-dose nebulized sodium cromoglycate reduced cough frequency by 31%.[29] In a crossover study of 41 patients treated with nalbuphine extended-release tablets (an opioid not currently available in Canada), there was a 52.5% placebo-adjusted decrease from baseline ($P<0.001$) at day 21. Not surprisingly, side effects such as nausea, fatigue, constipation, and dizziness were more common in the treatment arm.[30]

Conclusion

Chronic cough is a common and troubling symptom that severely affects the physical, social, and psychological well-being of our patients. An organized approach to diagnosis and treatment of any identifiable (and often multiple) conditions is important, rather than using multiple shotgun trials of therapy. If the cough is refractory or unexplained, there are still many effective therapies available. Speech and language therapy, along with neuromodulator treatments such as low-dose opioids, pregabalin, and gabapentin can be trialled. Resources are available for clinicians and patients at here. An algorithm to support decision making is shown in **Figure 1** and is available in the tools section of the Family

Physician Airways Group of Canada at www.fpagc.com. Empathetic counselling is important, as Family Physicians are often the last support for patients who have seen multiple consultants. New therapies offer hope for the future.

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