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Table of Contents

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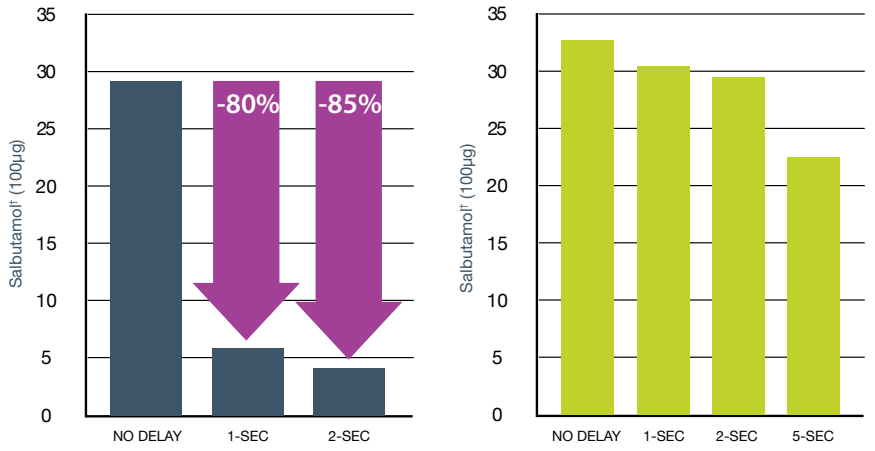

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1 Yang C et al, (2021): Canadian Thoracic Society 2021 Guideline update: Diagnosis and management of asthma in preschoolers, children and adults, Canadian Journal of Respiratory, Critical Care, and Sleep Medicine, DOI: 10.1080/24745332.2021.1945887. **2** Suggett J. Improved adherence and high patient satisfaction with 'on-the-go' spacer. Canadian Respiratory Conference 2023.

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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.

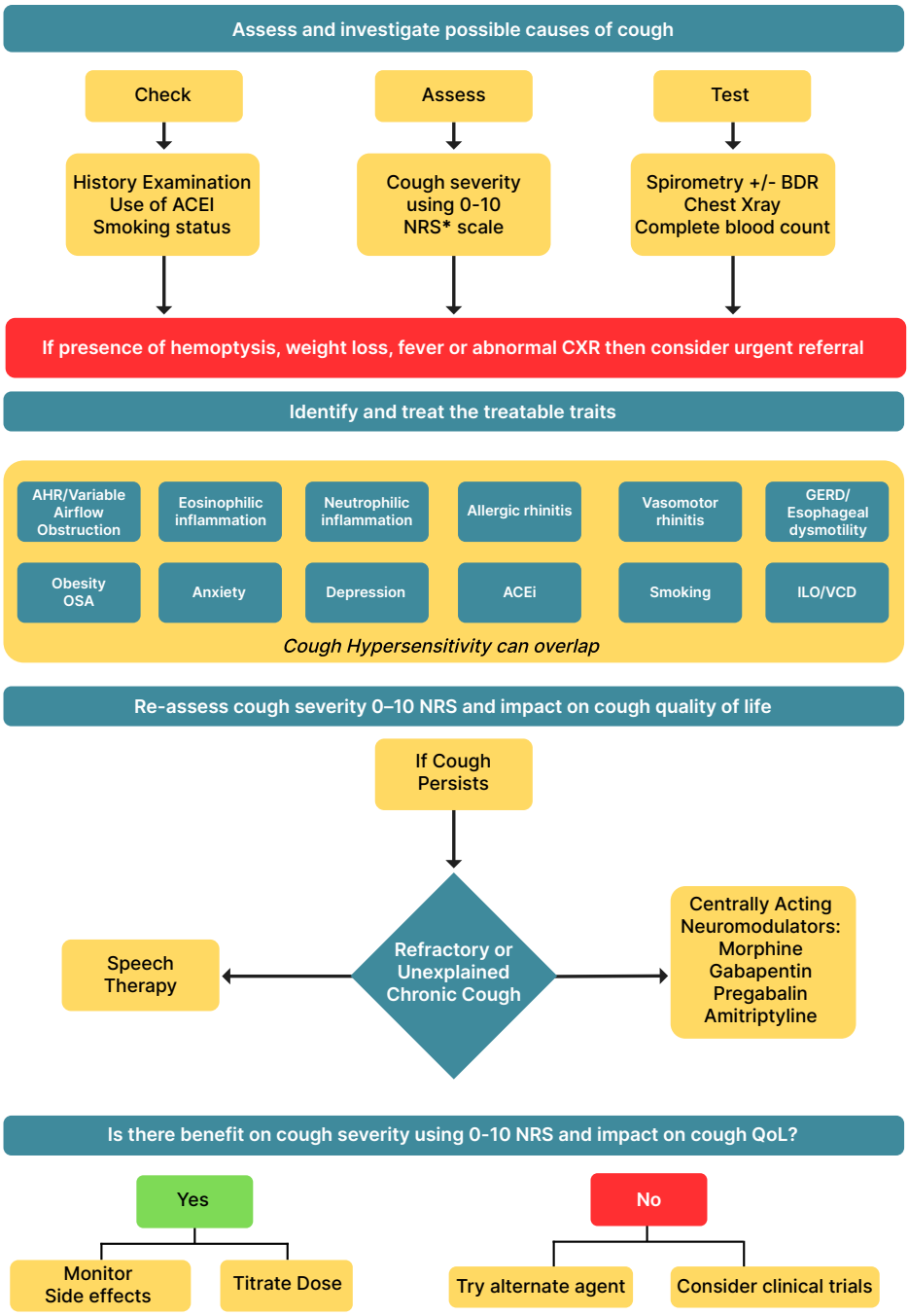

Figure 1. A clinical approach to the investigation and management of chronic cough. This algorithm guides clinicians through a series of steps, starting with an assessment of the patient's history and physical examination, followed by targeted diagnostic tests to identify treatable traits and potentially 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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Management of Bronchiectasis for the Community Respirologist

Giovanna Riolo, MD, Internal Medicine and Respirology

Introduction

Bronchiectasis is a common chronic lung disease that remains undertreated and under serviced, likely in part due to its heterogenous nature and diversity in clinical presentation. Bronchiectasis is characterized by the permanent dilation of the airways visible on radiographic imaging, characterized by decreased function of the mucociliary transport mechanism. This dysfunction leads to recurrent infections secondary to increased bacterial invasion and mucus accumulation. It is defined as a syndrome marked by chronic cough, sputum production, and repeated lower respiratory tract infections.[1,2] Bronchiectasis is an important area of respiratory medicine given its increasing prevalence. It affects an estimated 566 individuals per 100,000, making it the third most common chronic airway disease, after chronic obstructive pulmonary disease and asthma.[3] While it can develop in childhood, particularly during the pre-antibiotic era,[4] it can occur at any age, with prevalence increasing with advancing age. This increase in prevalence may be secondary to greater awareness amongst healthcare professionals.

Bronchiectasis is a treatable but rarely curable condition. Identifying and treating the underlying cause is recommended. Bronchiectasis can be caused by many underlying etiologies, including infectious, inflammatory, genetic, or immunological causes. Despite this wide range of etiologies, idiopathic bronchiectasis accounts for 32%–66% of all causes.[5] Treatment goals include managing any underlying systemic conditions, preventing lung infections, and implementing chest physiotherapy. Surgery may be recommended for localized bronchiectasis with refractory infections and hemoptysis. This article will review the chronic management of bronchiectasis, with a focus on chest physiotherapy techniques and the use of inhaled antibiotics.

Chest physiotherapy helps expectorate sputum and is the mainstay of therapy. It should be recommended for all patients irrespective of the etiology of bronchiectasis. It includes techniques such as postural drainage, deep breathing exercises, percussion, and the use of positive expiratory pressure devices. Postural drainage relies on gravity to drain mucous from the uppermost lung lobes, while deep breathing followed by forced expiratory manoeuvres, known as the "active cycle of breathing" technique, allows secretions in the dilated bronchi to gravitate toward larger airways for clearance. Percussion of the chest wall, performed manually with cupped hands or using oscillating devices,

aids in loosening and dislodging sputum. These techniques should be performed for a minimum of 5 to 10 minutes twice daily. When efficiently performed, chest physiotherapy can reduce cough and sputum production, thereby reducing the risk of pulmonary infections.

Pseudomonas aeruginosa (Pa) is the most common pathogen isolated in the sputum of patients with bronchiectasis airways.[6,7] Chronic infection, defined as isolation of Pa in sputum cultures on at least two or more occasions, spaced at least 3 months apart over a one-year period,[8] is difficult to eradicate even with the use of broad spectrum intravenous (IV) antibiotics.[9] Once established, chronic Pa forms biofilms, which are thin layers of bacteria within an extracellular polymeric matrix. They form colonized surfaces in airways, which are associated with greater airway inflammation and an increased risk of exacerbations that potentially require hospitalization, and increased mortality compared to non-pseudomonas.[6,7] This infectious process perpetuates the bronchiectasis cycle. Biofilms inhibit the clearance of bacteria by the host immune system and reduce antibiotic penetration, favouring microbial persistence.[10] As a result, international guidelines recommend long-term antibiotic treatment for patients with chronic Pa infection and frequent exacerbations.[1]

Inhaled antibiotics targeting Pa, such as inhaled colistimethate sodium or inhaled tobramycin, deliver high concentrations of medications directly to the airways, the primary site of infection, providing greater efficacy while minimizing side effects and reducing the risk of antibiotic resistance.[11] A study by Haworth et al., known as PROMIS-I, was a double blind, randomized, placebo-controlled trial evaluating inhaled colistimethate sodium in adults with non-cystic fibrosis bronchiectasis.[12] Conducted across multiple hospitals in 12 countries (Australia, Belgium, Germany, Greece, Israel, Italy, Netherlands, New Zealand, Portugal, Spain, Switzerland, and the UK), the study enrolled patients who had at least two pulmonary exacerbations requiring oral antibiotics or one intravenous antibiotic in the preceding year.[12] Inhaled colistimethate sodium showed a 21% reduction in exacerbations and a 52% reduction in severe exacerbations compared to placebo.[12] Statistically significant improvements were also observed in the frequency of exacerbations, the study's primary outcome, along with a significant reduction in severe exacerbations and a significant improvement in quality of life, measured using the St. Georges Respiratory Questionnaire.[12] These findings have contributed to international guideline recommendations supporting the use of inhaled antibiotics to patients with bronchiectasis, chronic Pa infection, and frequent exacerbations.[1]

Colistimethate sodium, also known as colistin, is supplied as a powder in a vial and can be stored at room temperature. For reconstitution, add 2 mL of sterile water to the vial and 1 mL (equivalent to 75 mg) is drawn for inhalation. To increase volume for nebulization, an additional 2 mL of saline can be added to nebule along with the above mixture. The unused portion should be refrigerated for use in the second dose of the day. The standard dosing regimen is 75 mg inhaled twice daily.

Inhaled tobramycin can also be used to treat or prevent Pa infections, with the main goal of improving or maintaining lung function. As an aminoglycoside antibiotic, tobramycin binds irreversibly to the bacterial 30S ribosomal subunit, thereby inhibiting the initiation of protein synthesis, resulting in bacterial cell death.[13] The 2015 study by Orriols et al. demonstrated that following a 3-month course of inhaled tobramycin, clearance or eradication of Pa was sustained for 12 months in 54.5% of patients.[14] While definitions of eradication vary across studies, it is generally defined as the absence of Pa detection in sputum at a specified time point during the study.[15] Eradicating Pa was associated with a significant reduction in exacerbation frequency, fewer hospitalizations, and shorter hospitalization durations.[15] A literature review of inhaled tobramycin revealed that in five of seven studies, spirometry outcomes remained stable, showing neither significant improvement nor decline.[15] The overall results suggest that eradication, though sometimes transient, was achieved in 22%–55% of patients treated with inhaled tobramycin.[15] Even a simple reduction in Pa density, without complete eradication, can lead to clinical improvement.[13]

Inhaled tobramycin is generally well tolerated by most patients. However, side effects can include hoarseness, increased cough and sputum production, dyspnea, wheezing, pharyngitis, and fatigue.[16] The use of salbutamol may mitigate these side effects. In the study by Loebinger et al. a decline in renal function was observed in 8% of patients, along with reports of mild, transient hearing loss, tinnitus, and occasional cases of

moderate labyrinthitis.[17] For adults with non-cystic fibrosis bronchiectasis, the recommended inhaled dose of tobramycin is 80 mg inhaled twice daily via nebulizer. This can be nebulized along with 0.5 to 1 mL (2.5 mg to 5 mg) of undiluted salbutamol. Prior to initiating therapy, a spirometry test can be carried out before a test dose of inhaled tobramycin. A post spirometry test can be used to evaluate for tolerance and to detect any significant decreases in force expiratory volume in one second (FEV_1) or forced vital capacity (FVC) prior to prescribing inhaled antibiotics. Patients may continue to use inhaled tobramycin as long as it is tolerated and chronic Pa persists in sputum cultures. Once therapy has been initiated, periodic monitoring of sputum cultures and side effects with audiometry tests, blood work (creatinine), and evaluation of symptoms should be implemented.

Conclusion

Improving tracheobronchial clearance should be considered as the mainstay of therapy in bronchiectasis. In cases of chronic Pa, inhaled antibiotics have been incorporated into guidelines for both chronic suppression[18,19] and eradication of Pa.[1] These therapies have become central to improving quality of life for these patients. Facilitating research into the various subtypes of bronchiectasis may help determine the optimal care for these patients and provide a multidisciplinary approach to treatment.

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The Air We Share: Guiding Inhaler Selection Today for a Sustainable Tomorrow

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Introduction

Climate change is currently the greatest global health threat.[1] As the planet experiences rising temperatures due to global warming, widespread health impacts are emerging, including extreme weather events, food insecurity due to droughts, and forced relocation of populations.[2] From a respiratory health perspective, patients with lung disease experience negative health consequences due to high temperatures, risks from heat-related illnesses, exposure to wildfire smoke that causes poor air quality, and increased severity and duration of pollen seasons.[2] The resulting health consequences contribute to increased use of healthcare services, which in turn generate their own contributions to healthcare pollution, thus further worsening the climate crisis.

In fact, the health sector contributes more than 5.2% of net global greenhouse gas emissions.[2] In Canada, healthcare activities are responsible for 4.6% of the country's total greenhouse gas emissions,[3] placing Canada's healthcare system among the top four emitters per capita by country.[4] In terms of the contributions of various healthcare sectors to greenhouse gas emissions, England's National Health Service (NHS) demonstrated that anesthetic gases and metered dose inhalers (MDIs) play a significant role;[5] MDIs alone contribute to 3.1% of the NHS's total healthcare emissions.[6] MDIs rely on hydrofluorocarbon (HFC) propellants to deliver medication, which act as potent greenhouse gases when released into the atmosphere. Depending on the formulation, one aerosol inhaler can have a carbon footprint equivalent to driving a gasoline-powered car up to 170 km.[7] In Canada, short-acting beta-agonist (SABA) inhalers constitute 71% of total inhaler use,[8] the majority of which are delivered via MDI devices. For these reasons, strategies that reduce the use of MDIs have the potential to reduce negative environmental consequences of respiratory care.

However, it is important to recognize that healthcare delivery itself contributes to greenhouse gas emissions, with significant contributions related to the healthcare supply chain and the infrastructure required to deliver care, such as energy use in buildings, waste generation, and water consumption.[5] The carbon footprint of healthcare increases with the intensity of services delivered; for example, a single admission to a critical care bed is estimated to produce approximately 90 times more greenhouse gas emissions compared with a routine physician office visit.[5,9] Thus, there are opportunities to reduce the impact of climate change on the environment through reducing overall healthcare needs.

While much attention has been given to preferentially selecting inhalers that have the potential to reduce greenhouse gas emissions, it is equally important to consider how optimal inhaler selection can improve respiratory disease control. By reducing SABA use, minimizing exacerbations, and decreasing healthcare encounters, appropriate inhaler choices can maximize patient outcomes while also delivering environmental co-benefits. With this in mind, the Canadian Thoracic Society (CTS) proposed several opportunities to reduce inhaler-related greenhouse gas emissions in its Position Statement on Climate Change and Choice of Inhalers for Patients with Respiratory Disease.[10] This article summarizes these considerations and outlines the Climate Conscious Inhaler Prescribing Sustainability Pathway provided by CASCADES and adapted by Green et al. (**Figure 1**), to support respirologists in prescribing practices that are both sustainable and optimize patient outcomes.[11]

Ensure the Correct Diagnosis

Studies have demonstrated that 30–60% of patients with physician-diagnosed chronic obstructive pulmonary disease (COPD) do not have the disease.[12] Similarly, 33% of patients with physician-diagnosed asthma lack objective evidence of asthma, yet 79% of these patients continued to use asthma medications.[13] For these reasons the CTS's Choosing Wisely statements encourage conscientious medication prescribing. This includes avoiding the continuation of asthma medications in individuals who have not demonstrated clear clinical benefit or confirmation of reversible airflow limitation, and by refraining from initiating long-term maintenance inhalers in stable patients with suspected COPD unless post-bronchodilator airflow obstruction has been confirmed with spirometry.[14] As respirologists, it is our duty to advocate for objective confirmation of respiratory disease to guide appropriate inhaler prescribing and use, and to consider discontinuing inhaled therapies when objective testing does not confirm disease and the patient has not derived clinical benefit.

Optimize Disease Control

Uncontrolled asthma is associated with increased healthcare resource utilization,[15] while overuse of SABA in patients with asthma is associated with increased rates of exacerbations and mortality.[16] It is therefore not surprising that patients with poorly controlled asthma are estimated to have a carbon footprint nearly three times higher than those whose asthma is well-controlled.[17] Thus, adherence to guideline recommendations that optimize disease management is key to reducing the carbon footprint of care. Notably, the Global Initiative for Asthma no longer recommends SABA-only treatment for adults and adolescents with asthma, citing evidence that SABA monotherapy increases the risk of severe exacerbations and asthma-related death.[18] Instead, it supports the use of symptom-driven or daily inhaled corticosteroid-containing controller treatment.[18] Meanwhile, an evaluation of budesonide/formoterol dry powder inhaler (DPI) showed a 95.8% reduction in carbon emissions compared to as-needed salbutamol delivered through MDI and a 93.6% reduction compared to a regimen of budesonide DPI plus as-needed salbutamol MDI.[19] These findings reinforce that adhering to guideline-recommended care not only improves patient outcomes but also has a positive environmental impact.

Similarly, patients with COPD who experienced two or more severe exacerbations contribute greenhouse gas emissions up to 7-fold higher than those without exacerbations.[20] The 2023 CTS Guideline on Pharmacotherapy in Patients with Stable COPD and the 2025 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report both provide management recommendations to reduce exacerbations through escalation of inhaled therapies in accordance with symptoms and exacerbation risk.[21,22] Inhaled triple therapy combinations have been shown to reduce all-cause mortality, and both guidelines recommended delivering combination therapy using a single inhaler

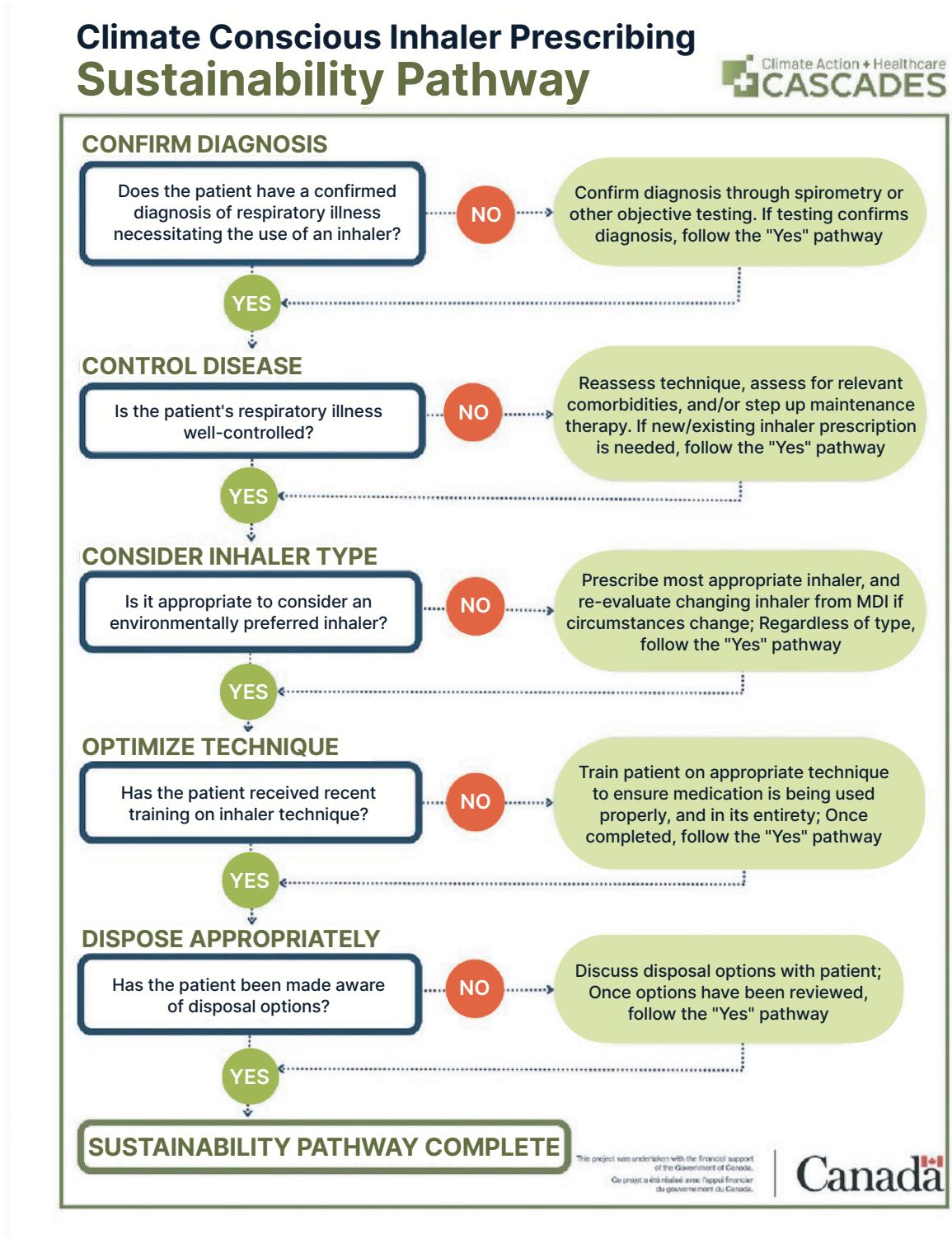

Figure 1. Strategies for Respirologists to Reduce Carbon Emissions Associated with Inhalers; *adapted from CASCADES' Concious Inhaler Prescribing in Outpatient Care, version 3.0;* https://cascadescanada.ca/resources/sustainable-inhaler-prescribing-in-primary-care-playbook *(CC BY-NC-SA 4.0).*

instead of multiple inhalers when possible.[21,22] This approach simplifies treatment and also reduces the overall number of dispensed inhalers, offering an added environmental co-benefit. As such, adhering to guideline-recommended therapy improves patient care outcomes while also reducing the environmental footprint related to the disease. Respirologists play an important role in optimizing disease control and educating both patients and referring providers on guideline-based care.

Choose Inhalers Wisely

As outlined in the CTS Position Statement and the accompanying Choosing Wisely statement, once a respiratory diagnosis is confirmed and inhaler therapy is indicated, providers can decrease the environmental footprint of care by prioritizing inhalers that generate lower greenhouse gas emissions when initiating new controller or rescue therapy.[10] DPIs and soft mist inhalers have a carbon footprint approximately ten times lower than that of MDIs.[23] Many medications available in MDIs are also offered in alternative inhaler forms within the same drug class and are often preferred by patients.[24,25] Recognizing that MDIs remain necessary and important for specific patient populations, including children, older adults, and those with concerns about adequate medication delivery using non-MDI devices, providers can select MDIs that use lower-impact greenhouse gas propellants (HFC-134a rather than HFC-227ea) or those with smaller metered valves that deliver a lower volume of HFCs (e.g., Teva-Salbutamol or Airomir) to reduce emissions.[10,26]

What the CTS Position Statement emphasizes, but is not always considered in practice, is that the decision to preferentially select inhalers that have a lower carbon footprint is contingent on shared decision-making with the patient. This includes consideration of key factors impacting adherence, including patient preference, cost, ease of use, and inhaler technique.[10] As such, automatic switching from MDIs to alternative inhalers is not recommended without careful consideration of the potential impact on the patient's ability to use the medication and timely reassessment of disease control. Respirologists should advocate for prescribing the inhaler that best controls the patient's underlying disease regardless of device type, while also considering opportunities to preferentially select lower-emission inhalers when all other factors are equal.

Optimize Inhaler Technique

It is well-known that inhalers are frequently used incorrectly, and that inhaler misuse is associated with poor disease control.[27,28] For MDIs, errors often occur in the context of poor synchronization of actuation with inhalation.[26] Ensuring proper inhaler technique, through frequent education and encouraging the use of spacers with MDIs, can improve drug delivery, ensure better disease control, reduce overuse of SABAs, lower exacerbation rates, and decrease greenhouse gas emissions.[10,28,29] Respirologists should routinely verify inhaler technique with their patients and engage allied health professionals in providing continuous patient education.

Dispose Appropriately

There is ongoing recognition that disposing of inhalers in landfills is problematic. The plastic components degrade poorly, and the HFC propellants used in MDIs are potent greenhouse gases. Unfortunately, MDI devices are often disposed before they are fully used, either because they are expired, no longer needed, or if patients are unable to determine if the inhaler is empty, particularly when embedded dose counters are absent. A study from the UK found that 75% of MDIs without dose counters were discarded before they were empty, with one-third containing >50% of their original doses.[30] Surveys conducted in both British Columbia and the United Kingdom have revealed that only a minority of respondents return empty inhalers to local pharmacies for disposal, with the majority disposing them in household waste.[30,31] Meanwhile, many hospitals send inhalers for incineration with other medical waste. These practices identify a need for more accessible and sustainable approaches to inhaler recycling. Companies such as 'Go Zero' facilitate sustainable recycling through the provision of recycling boxes for inhalers and their associated materials.[32] Once collected, recycled MDIs are disassembled into

various components, such that plastics and metals are recycled and any remaining propellants or medications are extracted and neutralized. Respirologists play an important role in this effort by educating patients regarding proper inhaler disposal and recycling practices, and advocating for improved inhaler recycling methods at their workplaces.

Future pMDIs

Looking to the near future, the development of MDIs containing next-generation propellants with near-zero global warming potential is highly anticipated. For example, one such propellant, HFO-1234ze(E), has a global warming potential 99.9% lower than current propellants, enabling MDIs using this propellant to achieve a carbon footprint similar to that of a DPI.[33] These next-generation propellants will be critical to providing maximal inhaler choice while reducing the carbon footprint of MDI use. Respirologists should advocate for access to these novel inhalers and stay informed about their clinical applications.

Conclusion

In summary, as climate change increasingly threatens global health, with a disproportionate impact on patients with respiratory disease, respirologists play an important role in advocating for sustainable inhaler prescribing. This multifaceted approach includes confirming the diagnosis, optimizing disease control, considering the carbon footprint of various inhaler types, ensuring proper technique, and supporting appropriate disposal of inhalers. Guideline adherence helps ensure that respiratory diseases are optimally treated to reduce the risk of exacerbations, reduce SABA overuse, and lower healthcare utilization, all of which are associated with environmental co-benefits. Importantly, switching patients to lower-emission inhalers should not be automatic; rather, it should involve shared decision-making with patients, which considers that the selected inhaler is affordable, available, and usable. Ultimately, the inhaler that best optimizes the patient's respiratory disease is likely to have the most positive impact on climate sustainability.

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Cardiopulmonary Collaboration in Respiratory Care: Shifting the Paradigm

Pierre Landry, MD

Our Patients Do Not Exist in a Vacuum—Their Care Should Not Either

In recent years, the management of chronic obstructive pulmonary disease (COPD) has evolved from a symptom driven focus to prioritizing the reduction of exacerbations, with a view to preventing morbidity and mortality. This treatment landscape continues to evolve, with biologic therapies on the horizon that promise to substantially alter the current paradigm centred on inhaled therapies. While other jurisdictions have approved dupilumab and mepolizumab as add-on therapies to prevent COPD exacerbations, these options are not yet approved for use in Canada. Regardless of regulatory status, the foundation of COPD therapy remains the same: triple inhaled therapy, combined with inhaled corticosteroids, long-acting anti-muscarinic agents, and long-acting beta-agonists. At the time of enrolment in the studies, single inhaler triple therapy (SITT) was not yet the standard of care; however, the majority of enrolled patients (over 98%) were receiving all three components.[1,2] While multiple inhaler triple therapy was permitted, both studies demonstrated a statistically significant reduction in COPD exacerbations.[1,2] Biologics are intended as an add-on to baseline therapy, yet many patients remain undertreated and lack access to SITT.

Our Canadian COPD guidelines have emphasized a clear preference for SITT, advocating for its rapid initiation in highly symptomatic patients, and those at increased risk of exacerbations.[3] SITT has been demonstrated to reduce exacerbations and mortality, contributing to a reduction in hospitalizations and emergency department visits.[3] Nevertheless, many patients remain on inadequate therapy and continue to face an elevated risk of exacerbations, thus predisposing them to increased mortality. In both the ETHOS and IMPACT trials, the most commonly adjudicated causes of death were cardiopulmonary in nature.[3-6]

Single inhaler therapy has been shown to be safe, effective, and economical. The number needed to treat (NNT) to prevent a moderate or severe COPD exacerbation is 1:4, while the number needed to harm (NNH) for pneumonia is 1:33.[3] Despite this favourable profile, there appears to be hesitancy regarding initiation of therapy. Whether this stems from regulatory barriers regarding access to medication, hesitancies based on risk perception pertaining to pneumonia or other adverse events, or gaps in knowledge, this is a situation which deserves urgent attention, in light of the simplicity and effectiveness of this intervention.

Beyond Breathing- Understanding Cardiopulmonary Risk

Exacerbations increase the risk of cardiopulmonary deaths[4-6] as well as elevate the risk of cardiac events. This signal is not associated solely with myocardial infarctions, but includes arrhythmias, congestive heart failure, and stroke.[4,5,7] Conversely, COPD exacerbations are frequently observed in patients admitted for cardiac issues. Exacerbations of either condition not only complicate but also potentiate hospital admissions. Compared to patients without comorbid heart failure, those with comorbid COPD and heart failure have a 1.61-fold higher risk of all-cause mortality, and 2.01-fold higher risk of COPD-related hospitalization.[8] Patients with COPD are also more likely to have risk factors such as hypertension and diabetes, while COPD itself is an independent risk factor for major adverse cardiac events, even in the absence of established cardiac disease.[7]

There are many plausible factors contributing to this association. While smoking is a common risk factor that is shared by both conditions, it is not the sole explanation. A complex interplay of many factors, including social determinants of health, along with certain biological and physiological factors has been proposed.[7] Cardiovascular causes of death are common across all stages of COPD, with the risk of adverse cardiac outcomes persisting for up to one-year post-exacerbation.[3] At milder and moderate stages of COPD, cardiovascular-associated deaths are more likely than respiratory related causes of death.[7]

Prior exacerbations are the strongest predictor of future exacerbations.[3,7] Additionally, an elevated symptom burden is associated with an increased risk of hospitalization in the next 12 months, and those with frequent productive cough appear to be at an increased risk of major cardiovascular events over the following 3 years.[7]

The relationship between cardiovascular and pulmonary outcomes are, as of yet, not fully understood. Proposed mechanisms revolve around a few factors: systemic inflammation spurred by underlying pulmonary inflammation, which may drive atherothrombosis; hyperinflation leading to reduced cardiac output and impaired oxygenation; and pulmonary vasoconstriction resulting in pulmonary hypertension, right ventricular dysfunction, and reduced cardiac output.[7]

COPD Exacerbations are Costly to Patients and Health Systems

COPD exacerbations are the second most common cause of hospitalization in Canada after childbirth,[9] and are projected to cost our healthcare system $1.5 billion annually.[10] In contrast to peripartum care, however, the average length of stay for a COPD admission is longer, at 7.2 days vs 2.2 days for peripartum care.[9] The annual direct cost per COPD patient is estimated to be between $3,910 to $6,690 (CAD), with combined total direct and indirect costs expected to exceed $9 billion by 2030.[11]

COPD remains a common comorbidity, affecting at least 10% of Canadian adults.[10] Despite this, COPD is underdiagnosed—current estimates suggest that approximately half of all cases remain undiagnosed. Those of us working in COPD care also recognize that misdiagnosis is common: many patients labelled with COPD show no evidence of airflow obstruction on spirometry,[12] and many others have not undergone spirometry testing to confirm their diagnosis. While hospitalization for COPD is increasing, associated mortality has declined;[13] however, it remains elevated, with an in-hospital and 90-day post discharge mortality rate of approximately 11.1%.[3] COPD exacerbations often result in irreversible lung function decline, and over half of patients hospitalized for an exacerbation die within 3.6 years of their first admission.[7] In our current Canadian healthcare climate, marked by persistent hospital overcrowding among other resource constraints, every attempt at preventing exacerbations should be undertaken.

Copd Care Faces Myriad Barriers

COPD care requires a multidisciplinary approach. Clinicians providing care for COPD patients span a wide spectrum, including family physicians, nurse practitioners, other internal medicine subspecialists, respiratory therapists, and nurses. It is likely that not all providers are aware of the serious repercussions of COPD exacerbations. Mortality risk is well established,[3] and a history of prior exacerbations is a strong predictor of subsequent exacerbations.[14] A 4 month delay in initiating triple therapy was associated with an increased risk of hospital readmission, both from COPD-related causes (15%), and all causes (22%), in addition to healthcare visits, overall healthcare costs, and the risk of disease progression.[14]

In the PRIMUS Study,[8] patients who experienced delays in initiating triple therapy were more likely to have a higher degree of baseline comorbidities and be covered by Medicaid.[14] This is replicated in the Canadian environment, where those with public drug coverage encounter many regulatory barriers to prompt SITT initiation, including requirements for mandatory waiting periods between therapeutic class escalations.[15] Drug coverage remains heterogeneous across the country owing to the provincial structure of healthcare provision, and the combination of private and public drug reimbursement schemes. Non-pharmacological interventions, including smoking cessation programs and pulmonary rehabilitation, are under-resourced and unavailable to many patients across the country.[7] This challenge is compounded by the fact that smoking remains the primary cause of COPD in Canada, and nicotine addiction is a major public health issue impacted by many factors including social determinants of health.

Furthermore, patients encounter barriers to accessing COPD care. Beyond frequent under or misdiagnosis, access to primary and specialty care is challenging for many patients. A substantial number of them lack a primary care provider, and respiratory medicine specialists are scarce. In Ontario, it was found that only 10% of patients with COPD receive a referral to a respirologist.[13] Accurate COPD diagnosis revolves around spirometry, yet this service is effectively unavailable in many parts of the country, owing to prolonged wait times and inefficient access.

System issues notwithstanding, patients face their own barriers. Non-adherence to prescribed therapies remains a major issue, as does poor health literacy.[8] On the provider side barriers exist as well, with therapeutic inertia and clinical nihilism impacting the quality of COPD care.[8] In addition, providing inappropriate therapy is also a major factor,[8] with many patients remaining undertreated for their disease.

Why Does This Matter?

We have therapies that are safe, effective, and simple to use that have been demonstrated to be cost effective.[13] These therapies have favourable side effect profiles, require no titration, and demonstrate efficacy across pulmonary and cardiac medicine. COPD exacerbations are common, they should be recognized as punctuations in the trajectory of illness, which can result in irreversible declines in health. It is time to acknowledge the public health importance of COPD, and its exacerbations, recognizing that their impact extends far beyond worsening pulmonary symptoms. Respirologists should champion these simple and effective interventions, and emphasize their importance to colleagues across the spectrum of medical subspecialties, as stakeholder involvement is key to reducing this public health burden.

Medical trainees and attending physicians alike can readily recite the four pillars of heart failure management and recognize the benefits of standardized medical therapies post myocardial infarction. These interventions are rote, and ingrained as standard of care, and cardiac rehabilitation is routinely offered at hospital discharge. Why then, do our patients with COPD leave hospital on ineffective and outdated therapies? Why does COPD care differ so markedly, given the close relationship with cardiovascular disease?

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