Volume 3, Issue 1, Spring 2025

ISSN 2817-416X (Print)
ISSN 2817-4178 (Online)

CANADIAN PRIMARY CARE TODAY

Clinical Insights, Perspectives, and Disease Management

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Canadian Primary Care Today is published 3 times per year in English and French.

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References: 1. Current Mounjaro Product Monograph. Eli Lilly Canada Inc. **2.** Data on File (First & Only). April 9, 2024.

doi.org/10.58931/cpct.2025.3138

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Essential Interstitial Lung Disease Management for the Primary Care Provider

Amanda Grant-Orser, MBBCh, FRCPC

Abstract

Interstitial lung diseases (ILDs) encompass a diverse group of disorders characterized by inflammation and fibrosis of the lung parenchyma. Despite their classification as rare, increasing evidence suggests ILDs are more prevalent than previously thought. Patients often present with respiratory symptoms such as exertional dyspnea, persistent cough, and fatigue. However, asymptomatic patients with incidental findings on imaging (e.g., interstitial lung abnormalities) are also common. Diagnosis relies on high-resolution CT (HRCT), pulmonary function tests, and detailed clinical evaluation. Respirology consultation is important for comprehensive management. The evolving ILD nomenclature, including progressive pulmonary fibrosis, aids in disease characterization and treatment planning. Management strategies include corticosteroids and steroid-sparing agents for inflammatory subtypes, while antifibrotic therapies (nintedanib, pirfenidone) are used for fibrotic and progressive disease. Non-pharmacological interventions, including pulmonary rehabilitation, smoking cessation, and vaccination, are critical for improving patient outcomes. Primary care providers play a pivotal role in early disease recognition, facilitating diagnostic testing, managing comorbidities, and coordinating specialist care. This review highlights the importance of timely diagnosis, evolving classifications, and emerging therapies, offering a collaborative framework for optimizing ILD care and outcomes.

Introduction

Interstitial lung diseases (ILDs), or pulmonary fibrosis, are a heterogeneous group of disorders characterized by inflammation and/or fibrosis of the lung parenchyma. This umbrella term encompasses diseases with similar clinical, physiological, radiological, and pathological features. Although often considered to include

Terminology	Presentation	Imaging	Management
Interstitial lung abnormalities	Incidental finding on CT in someone not known to have ILD	Terms may include reticulation, fibrosis, lung distortion, ground glass opacities, traction bronchiectasis, honeycombing, non-emphysematous cysts	Clinical assessment PFTs Respirology referral (especially when fibrotic features are present i.e. traction bronchiectasis, honeycombing, or progression)
Fibrotic ILDs			
Idiopathic pulmonary fibrosis	Older age, cough and dyspnea on exertion	UIP pattern: subpleural, reticulation, traction bronchiectasis ± honeycombing	PFTs, HRCT, Respirology referral
Autoimmune-ILD (aka SARD-ILD)	Presentation may vary	UIP, NSIP, fHP, or OP pattern	Co-management with PCP, respirology, and rheumatology
Fibrotic hypersensitivity pneumonitis	Indolent with progressive cough and dyspnea; Exposure to organic antigen detected in 50% (mold, bacteria, birds, among others)	fHP pattern: upper and mid lung Peribronchovascular fibrosis, traction bronchiectasis, mosaic attenuation	PFTs, HRCT Respirology referral
Occupational ILD	Exposure history to asbestos, silica, beryllium, metal dust, among others	Varies by exposure	Antigen avoidance PFTs, HRCT Respirology referral ± WSIB
Unclassifiable ILD	Presentation varies, often cough and dyspnea	Fibrosis in indeterminate pattern	PFTs, HRCT Respirology referral
Non-fibrotic ILD			
Non-fibrotic hypersensitivity pneumonitis	May be an acute presentation following exposure to an organic antigen (mold, bacteria, birds, among others)	Ground glass opacities, air trapping, centrilobular nodules	May require inpatient admission vs urgent respirology referral
Organizing pneumonia	Cough, dyspnea, fever, similar to pneumonia Non-responsive to antibiotics	Migrating opacities, central ground glass opacity surrounded by consolidation ring (Atoll sign)	Corticosteroids with taper over 3+ months, steroid-sparing agent may be required for relapse Respirology referral
DIP/ RB-ILD	Smoking related disease, rarely associated with an autoimmune cause	Centrilobular nodules, ground glass opacities	Smoking cessation Respirology referral

Terminology	Presentation	Imaging	Management
ILD phenotypes			
Progressive pulmonary fibrosis	Progression of symptoms, PFTs ± fibrosis on CT	Varies by disease subtype, fibrotic features usually present	Respirology referral
Familial pulmonary fibrosis	Two or more family members affected	Varies, may not be a typical radiologic pattern	PFTs, HRCT Respirology referral
Combined pulmonary fibrosis and emphysema	Smoking history, may not have obstructed PFTs, markedly reduced DLCO	Upper lobe emphysema and lower lobe fibrosis	COPD management Respirology referral for consideration of antifibrotic therapy

Table 1. Common types of interstitial lung diseases and select phenotypes. Other rare forms of ILD not included: lymphocytic interstitial pneumonia, sarcoidosis, pleuroparenchymal fibroelastosis, lymphangioleiomyomatosis, post-COVID-19 fibrosis, drug-induced ILD, and pulmonary alveolar proteinosis; *courtesy of Amanda Grant-Orser, MBBCh, FRCPC*

Abbreviations: aka: also known as; **ILD:** interstitial lung disease; **CT:** computed tomography; **PFTs:** pulmonary function testing; **UIP:** usual interstitial pneumonia; **HRCT:** high-resolution CT; **SARD-ILD:** systemic autoimmune rheumatic disease – ILD; **NSIP:** nonspecific interstitial pneumonia; **fHP:** fibrotic hypersensitivity pneumonitis; **OP:** organizing pneumonia; **PCP:** primary care physician; **WSIB:** workplace safety and insurance board; **DIP:** desquamative interstitial pneumonia; **RB-ILD:** respiratory bronchiolitis ILD; **DLCO: d**iffusion capacity for carbon monoxide; **COPD:** chronic obstructive pulmonary disease

over 200 different types, this estimate is likely exaggerated, as classical classification systems recognize fewer subtypes.[1] ILD is considered a rare disease, but recent prevalence studies suggest it may be more common than previously thought, with rates ranging from 20 to 108 per 100,000 at risk Canadians.[2,3] ILDs are typically categorized as either idiopathic or secondary to another underlying condition or precipitant.[4] ILD nomenclature can be confusing and is frequently updated—for example, the recent shift from "acute and chronic hypersensitivity pneumonitis (HP)" to "non-fibrotic and fibrotic HP".[5] Keeping abreast with these evolving classifications can be challenging without actively following the latest literature. Regardless of the subtype, when fibrosis is present, indicated by computed tomography (CT) radiologic features of honeycombing and traction bronchiectasis, the process is irreversible, and often progressive. Due to the chronic and progressive nature of many ILD subtypes, involving a respirologist in patient care is encouraged. This review summarizes current ILD nomenclature, highlights when to suspect ILD, suggests initial investigations to consider, outlines how respirologists approach cases, and discusses current management options for patients.

When to Suspect ILD and Initial Investigations

Patients with ILD typically present in one of two ways: either they are symptomatic, or the disease is identified incidentally through imaging. Common symptoms include a dry or occasionally productive cough, shortness of breath (particularly with exertion), and fatigue.[6] Due to smoking being a shared risk factor with other diseases like chronic obstructive pulmonary disease (COPD) and coronary artery disease, misdiagnosis is common.[7-9] Additionally, comorbid respiratory diseases with similar symptoms can make an accurate diagnosis difficult. Since inhaler therapy is ineffective in ILD, the diagnosis should be considered in patients who do not respond to conventional treatments. ILD may be "unmasked" by viral infections, therefore, persistent respiratory symptoms following an upper respiratory tract infection warrant further evaluation.[10] Age is also important, as ILD typically presents after the age of 50. However, it may appear earlier in those with an autoimmune or drug-related presentation.[11,12]

Certain risk factors, such as family history, increase the likelihood of ILD. Individuals with a family history of ILD (defined as two or more

affected relatives within the same pedigree) have an almost 30% chance of abnormal CT findings.[13,14] Although screening is not currently recommended, clinicians should maintain a high index of suspicion in symptomatic patients with crackles during examination and who have a relevant family history. Any rheumatic disease may manifest with ILD. The autoimmune diseases most frequently affected by ILD include scleroderma (25-45%), myositis (30-80%), and rheumatoid arthritis (10-30%).[15,16]

Incidental radiologic findings, termed interstitial lung abnormalities (ILAs), are becoming more common due to the growing use of CT imaging. ILAs can be detected during lung cancer screenings, coronary CT scans, nodule follow-ups, or even in the lower slices of abdominal CT scans and upper slices of head and neck CT scans. Although ILAs should be considered a significant incidental finding, their description is often not included in the "impression" section of reports and therefore may be missed.[17,18] Terms such as 'subpleural reticulation', 'fibrosis', 'traction bronchiectasis', and 'honeycombing' are important to identify.[19] In such cases, a detailed respiratory history, risk factor assessment, physical examination, pulmonary function tests (PFTs), and referral to respirology are recommended. ILAs may represent undiagnosed ILD and require longitudinal follow-up.[20]

Physical examination is valuable, as velcro-like crackles at the lung bases are present in up to 90% of cases and can be easily auscultated in even mild fibrotic disease with excellent observer agreement.[21-23] Inspiratory squeaks can indicate small airways disease, which is a feature of hypersensitivity pneumonitis.[24] Digital clubbing may occur in up to 50% of patients.[25] While PFTs are an essential test, they can be normal in mild ILD, making them unreliable for ruling out the disease.[26,27] Laboratory testing is nonspecific for ILD but can help in identifying autoimmune diseases through serologies such as rheumatoid factor, anti-citrullinated peptide, and antinuclear antibody, while extractable nuclear antigen and myositis serology testing should be considered on a case-by-case basis.[28,29]

The gold standard for diagnosing ILD is a high-resolution CT (HRCT) performed with an "ILD protocol," which includes inspiratory, expiratory, and prone imaging.[28] Chest radiographs are not recommended for ILD screening. HRCT should be considered for high-risk patients, including those with symptoms, a family history, autoimmune comorbidities, crackles on examination, restrictive PFTs, or abnormal chest radiographs suggestive of ILD. Patients with ILD on CT at the time of referral are often prioritized for respirology review, which significantly expedites their care.[7]

How Respirologists Diagnose ILD

Patients with ILD undergo a comprehensive evaluation upon referral to respirology, including a review of symptoms, timelines, precipitating events, and risk factors. Some practitioners may also use a questionnaire to identify environmental exposures that could contribute to the disease.[30] Baseline investigations might include liver function tests, infection screening, and autoimmune serologies to assess for comorbidities or prepare for medication initiation. PFTs, particularly forced vital capacity and diffusing capacity for carbon monoxide (DLCO), are useful for assessing disease severity, predicting mortality, and monitoring disease progression.[31,32] A six-minute walk test is helpful for evaluating exertional hypoxia, which may qualify some patients for home oxygen based on provincial eligibility criteria.[33] HRCT is essential for confirming an ILD diagnosis, and ideally, images should be reviewed by a thoracic radiologist. The radiologic pattern provides critical diagnostic insights into the ILD subtype. For instance, a usual interstitial pneumonia (UIP) pattern is observed in idiopathic pulmonary fibrosis (IPF), while nonspecific interstitial pneumonia (NSIP) may indicate autoimmune disease-related ILD, drug-induced ILD, or other conditions.[16,31,34]

Bronchoscopy is not routinely performed but may be used to rule out infection, assess for diffuse alveolar hemorrhage, or evaluate inflammatory markers (e.g., lymphocytosis on cell count and differential).[5,28] Transbronchial biopsy is not recommended to diagnose most forms of ILD, although may be useful in some clinical scenarios. Surgical lung biopsy is rarely performed and should only be considered after a case discussion in an ILD multidisciplinary discussion (MDD).[28] MDDs are a standard component of an ILD diagnostic workup, providing input from a team of experts.[35,36] While most ILD cases can be managed by general respirology, access to MDDs enhances diagnostic accuracy.[35] Virtual referrals to ILD programs, often located in tertiary care centres, are available in many regions to support community respirologists. These programs typically include specialized ILD physicians,

fellows, and allied health professionals. In addition, many community respirologists have undertaken dedicated ILD training.[37]

Patients with ILD are subsequently classified into specific subtypes[4] **(Table 1)**. Beyond traditional classifications, phenotypes are increasingly used to guide treatment. The term "progressive pulmonary fibrosis" (PPF) describes patients with worsening symptoms, PFTs, and/or imaging findings, who may benefit from antifibrotic therapies.[31] Familial pulmonary fibrosis is used to describe patients with a family history of the disease, who often experience a more aggressive disease course.[38] Combined pulmonary fibrosis and emphysema (CPFE) syndrome describes the simultaneous occurrence of COPD and ILD.[39] Novel endotyping techniques, including telomere length testing, genetic analyses, and predictive biomarkers, hold promise for ILD management but are currently limited to tertiary ILD programs or research settings.[40-42]

Current and Emerging Therapies for ILD

Management of ILD involves both pharmacological and non-pharmacological approaches. For inflammatory subtypes, such as autoimmune disease-related ILD, non-fibrotic hypersensitivity pneumonitis, or drug-induced ILD, corticosteroids are often initiated, followed by steroid-sparing agents like mycophenolate or azathioprine.[43,44] Fibrotic and progressive disease subtypes, including IPF and PPF, are treated with antifibrotic medications.[31] Currently, two antifibrotics are approved for use to slow the progression of ILD: nintedanib (Ofev), indicated for IPF and PPF, and pirfenidone (Esbriet), approved for IPF.[45-47] Both require liver function monitoring and may cause gastrointestinal side effects, limiting their tolerability. Symptom management, such as treating cough with over-the-counter suppressants, liquid codeine, or low-dose morphine, is also common.[48] Proton pump inhibitors are only recommended for those with

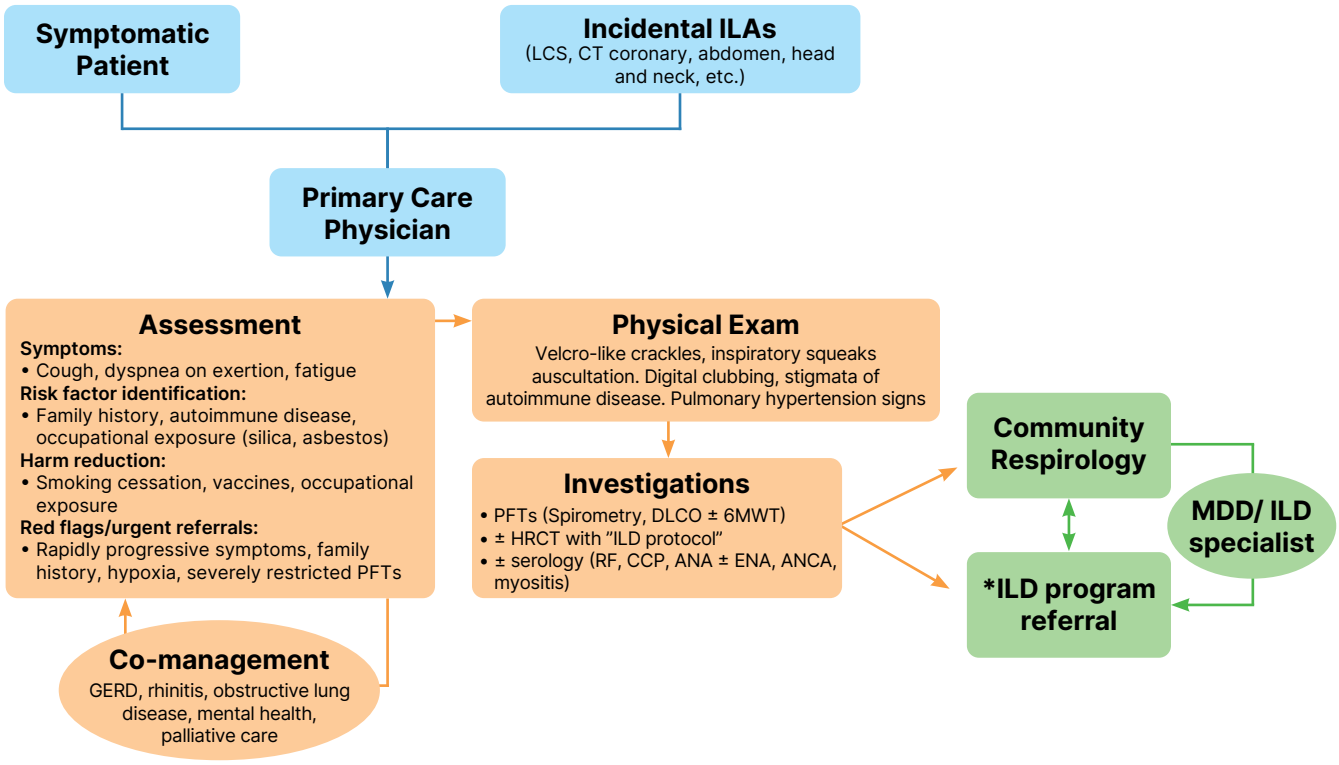

Figure 1. Suggested algorithm for ILD work up and referral; *courtesy of Amanda Grant-Orser, MBBCh, FRCPC*

*Referral patterns and access to ILD programs may vary by region

Abbreviations: ILAs: interstitial lung abnormalities; **PFTs:** pulmonary function testing; **DLCO:** diffusion capacity of carbon monoxide; **6MWT:** six-minute walk test; **HRCT:** high-resolution computed tomography; **ILD:** interstitial lung disease; **RF:** rheumatoid factory; **CCP:** Anti-citrullinated protein; **ANA:** antinuclear antibody; **ENA:** extractable nuclear antigen; **ANCA:** antineutrophil cytoplasmic antiody; **MDD:** multidisciplinary discussion; **GERD:** gastroesophageal reflux disease.

symptomatic reflux disease.[49] For advanced or progressive disease, lung transplantation may be considered.

Non-pharmacological management focuses on risk factor modification. Patients with hypersensitivity pneumonitis are advised to avoid exposure to antigens.[50] Smoking cessation is essential as it may slow the progression of ILD and mitigate the synergistic risk of developing lung cancer associated with smoking and ILD.[51] Vaccinations, including those for influenza, COVID-19, and pneumococcal infections are strongly recommended. Respiratory syncytial virus (RSV) vaccination should also be considered. While home oxygen therapy does not improve survival, it enhances quality of life.[52] Pulmonary rehabilitation and early referral to palliative care are similarly beneficial and encouraged.[53-55] Patient support groups are available through the Canadian Pulmonary Fibrosis Foundation (cpff.ca).

How Can Primary Care Providers Co-Manage ILD?

Primary care is the cornerstone of Canadian healthcare and often the first point of contact for patients with ILD **(Figure 1)**. Early suspicion by primary care physicians (PCPs) is crucial for improving care, enabling timely testing (e.g., PFTs, HRCT) and referral to respirology. PCPs play a key role in addressing risk factors, including promoting vaccination, smoking cessation, and reducing occupational exposures. They also frequently manage comorbid conditions such as gastroesophageal reflux disease (GERD), postnasal drip, and asthma. Additionally, PCPs assess mental health, provide palliative care support, or facilitate access to such services, which are essential in ILD. Advocating for patients, coordinating with specialists, and fostering clear communication significantly enhances patient care and outcomes.

Conclusion

In summary, early recognition and appropriate testing for ILD are critical responsibilities for PCPs. By maintaining a high index of suspicion, identifying risk factors, initiating key diagnostic tests such as PFTs and HRCT, noticing incidental radiologic findings and facilitating timely referrals to respirology, PCPs can significantly impact patient outcomes. Additionally, addressing comorbidities, advocating for lifestyle modifications, and providing palliative care when needed ensure comprehensive, collaborative care for patients with ILD.

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Financial Disclosures

A.G.O.: Honoraria: Boehringer Ingelheim.

Resources

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Canadian Thoracic Society Guidelines and Position Statements
CTS guideline library
cts-sct.ca/guideline-library

American Thoracic Society Guidelines
ATS Official Documents, Interstitial Lung Disease
www.thoracic.org/statements/insterstitial-lung-disease.php

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doi.org/10.58931/cpct.2025.3139

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

Alan Kaplan, MD, CCFP(EM), CPC(HC)

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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Financial Disclosures

A.K.: Advisory board/Speakers bureau: ALK, AstraZeneca, Boehringer Ingelheim, Cipla, Covis, GSK, Merck Frosst, Moderna, Novartis, NovoNordisk, Pfizer, Sanofi, Teva, Trudell, and Valeo

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doi.org/10.58931/cpct.2025.3140

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Menopause Hormone Therapy in 2025

Susan Goldstein, MD, CCFP, FCFP, MSCP

Introduction

Menopause is, in fact, a single day officially marked one year after the cessation of menses. It is followed by post menopause which can last for half of a women's adult life! Menopause typically occurs between the ages of 46 and 52 years with an average age of 51.[1] It signifies the end of reproductive function, and is marked by fluctuating and declining hormone levels, which can lead to a range of often distressing symptoms. The perimenopause is the transition phase that precedes menopause, lasting up to 10 years. For many women, menopausal symptoms may first appear later in the perimenopause. While we use the term "women", guidance applies to all patients who experience menopause, even if they do not identify as a woman.

When people use the term "menopause" they are usually referring to the "climacteric", a period which includes the perimenopause, menopause, and early post menopause stages.

In Canada, over 2.5 million women are between the ages of 45 and 55, and up to 80% of them will experience menopause-related symptoms. There are now over 30 validated symptoms of menopause, some of which can have a significant impact on function and quality of life. A recent study by the Menopause Foundation of Canada reported that up to 10% of women will leave the workforce due to unmanaged menopausal symptoms.[2]

The most impactful symptoms of menopause include vasomotor symptoms (VMS) which include hot flashes and night sweats, sleep and mood disturbances, memory issues, muscle and joint pains, and symptoms of the Genitourinary Syndrome of Menopause (GSM) such as vaginal dryness, bladder issues, and sexual dysfunction. Recent evidence has shown that frequent or severe menopausal vasomotor symptoms are linked to a higher risk for illnesses including cardiovascular disease and diabetes.[3]

The Menopause Quick Six Questionnaire: If a patient answers yes to question 1, they may be perimenopausal or menopausal and further clarification should be obtained. A "yes" to question 2,3, or 4 may indicate symptoms amenable to treatment with Menopausal Hormone Therapy (MHT) or other therapies. A "yes" to question 5 or 6, while not indications for MHT, do indicate relevant symptoms that should be considered when formulating your menopausal treatment plan.

Figure 1. The Menopause Quick Six Questionnaire.[4]; *Reproduced with permissions. Goldstein, Susan. An efficient tool for the primary care of menopause, Canadian Family Physician, April 2017, 63(4):297-298. Accessed April 1, 2025. Available from: https://mq6.ca/mq6-fillable-tool-2/*

Assessing the Need for Menopause Hormone Therapies

Healthcare professionals continue to face challenges with assessing and managing perimenopausal and postmenopausal patients. Lack of time, education, remuneration, and available tools are just some of the obstacles to providing effective care.

Consider starting the discussion about menopause with your patients in their early to mid-40s to help them prepare. A quick and effective approach is to use the Menopause Quick Six (MQ6) assessment tool **(Figure 1)**.[4] Featuring open-ended questions, this tool facilitates conversations and screens for common menopausal symptoms that can be addressed with menopause-specific treatments. A binary-version of the tool can also be found online for patients to self-administer prior to their visit here.

Menopause Hormone Therapies

Menopause hormone therapies include both systemic and local vaginal therapies. The term menopause hormone therapy (MHT), previously known as hormone replacement therapy (HRT), commonly refers to the use of *systemic* hormone therapy.

MHT is indicated to treat VMS, GSM, hypoestrogenic states, and for the prevention of osteoporosis.[1,5,6] Typical MHT regimens include a combination of an estrogen and a progestogen (EPT).

Estrogens provide the main symptom relief from vasomotor symptoms and are available in oral and transdermal formulations (patches and gels). Commonly used systemic estrogens include estradiol (*E2*) and conjugated estrogen. Estetrol, (*E4*) found in a newly developed contraceptive, is being studied for use in MHT.

Progestogens provide uterine protection against estrogen-induced endometrial hyperplasia and include micronized progesterone and synthetic progestins. The 52 mcg LNG-IUS (levonorgestrel containing intrauterine system) may be used *off-label* to safely provide up to 5 years of endometrial protection when used with estrogen in an EPT regimen.[7]

Some women may experience intolerance to progestogenic side effects such as bloating, headache, mood changes, and breast pain. Options include using micronized progesterone vaginally (off-label), long-cycle EPT regimens, and newer products that do not require the addition of a progestogen (i.e., the Tissue Selective Estrogen Complex (TSEC)-CEE/BZA and the Selective Tissue Estrogen Activity Regulator (STEAR)-Tibolone).

Local hormone therapies to treat GSM include vaginal estrogen creams, rings, inserts, and vaginal dehydroepiandrosterone sulfate (DHEAS). A newer oral medication ospemifene, from the class of selective estrogen receptor modulators, has been developed for women who prefer not to use local vaginal products or find it difficult to apply treatments vaginally.

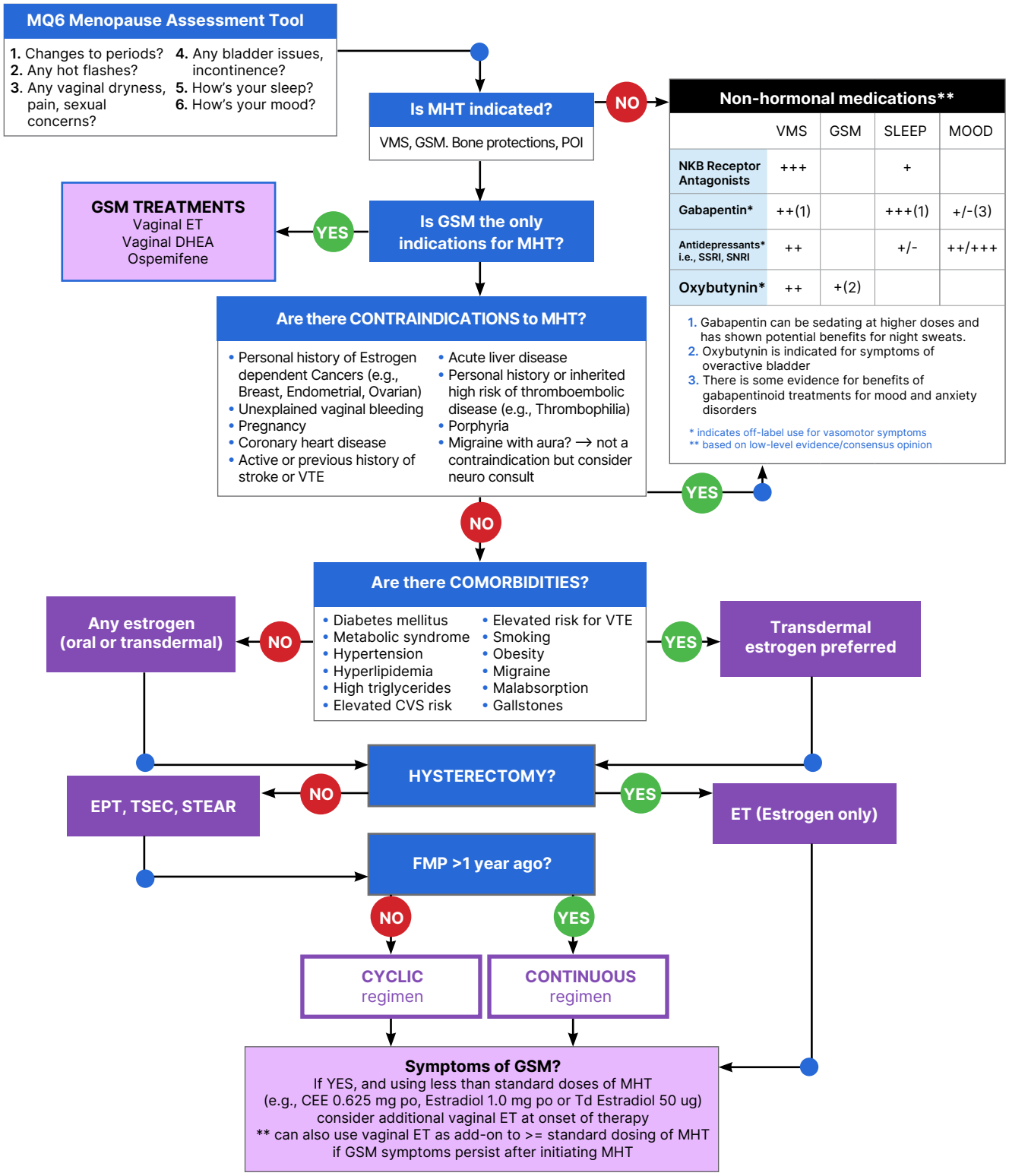

Figure 2. The MQ6 Treatment Algorithm[4]; *Reproduced with permissions. Goldstein S. An efficient tool for the primary care of menopause. Can Fam Physician. 2017; 63(4):297-298. The tool is available from: https://mq6.ca/mq6-interactive-algorithm/#algorithm*

Abbreviations: MHT: Menopausal Hormone Therapy; **EPT:** Estrogen + Progestogen Therapy; **ET:** Estrogen Therapy; **FMP:** final menstrual period **Td:** Transdermal; **POI:** Premature Ovarian Insufficiency; **GSM:** Genitourinary Syndrome of Menopause; **VMS:** Vasomotor symptoms; **TSEC:** Tissue Selective Estrogen Complex; **STEAR:** Selective Tissue Estrogenic Activity Regulator; ***Cyclic regimen:** a daily estrogen with a progestogen added 12-14 days of the month **NKB Receptor Antagonist:** Neurokinin B Receptor Antagonist

Patients frequently request 'bio-identical' hormones, typically referring to custom-compounded hormones. However, their use is discouraged by most menopause guidelines.[1,5,6] For women seeking compounds similar to naturally produced hormones, options such as estradiol, estetrol, and micronized progesterone are considered body-identical.

Tables of products available in Canada can be found in the Canadian Menopause Society Menopause Management Pocket Guide here.

How do the Guidelines Support Management?

After decades of use, the prescribing of MHT halted after the 2002 Women's Health Initiative (WHI) study findings, which reported increased risks of breast cancer, heart disease, and stroke in their cohort. However, these were women aged 50-80 (average age 63) without symptoms, the majority of whom were introduced to MHT after the age of 60 and/or many years post menopause. Two decades of cumulative data since the WHI study,[8] combined with a review of the original findings and recent research, have led to a new understanding of the WHI results, which now guide MHT prescribing in 2025.

National and international guidelines recommend initiating MHT in symptomatic women, without contraindications, who are under the age of 60 or within 10 years of the final menstrual period.[1,5,6]

An Approach to Prescribing MHT: Keeping it Simple

In 2025, the consensus among professional organizations advocates for a patient-centred approach to MHT. This approach begins with a risk assessment to rule out contraindications and to consider comorbidities, demographics, and patient preferences in order to provide an individualized treatment plan.[1,5,6] One approach includes using the Canadian evidence-based MQ6 Treatment Algorithm which supports the healthcare provider in creating a personalized treatment plan **(Figure 1)**.[4,9] The online interactive version of this decision tool can be found at here.

This treatment decision tool starts with reviewing indications for treatment, ruling out contraindications and then considering patient comorbidities to inform choice of regimen. While transdermal estrogens are not preferable for all patients, they are recommended for those with increased cardiovascular or clotting risks, or when timing or absorption may be problematic. The less thrombogenic micronized progesterone is also preferred over synthetic progestins when cardiovascular or breast risks are a concern.[1]

Also consider the reproductive stage, as treatment options differ when initiating therapy in perimenopausal versus postmenopausal women **(Figure 3)**.

Some women are unable or prefer not to take MHT and should be offered non-hormonal treatment options. Recent insights into the pathophysiology of hot flashes has led to the development of a new class of medications indicated for vasomotor symptoms, the Neurokinin B (NKB) Receptor Antagonists, which act locally in the brain, including in the thermoregulatory center, and have shown a reduction in vasomotor symptoms and improved sleep. Fezolinetant is the first-in-class agent from this new class available in Canada.

Other non-hormonal treatment options include the off-label use of SSRI/SNRI's, gabapentin, and oxybutynin, as well as menopause-specific cognitive-behavioural-therapy or hypnosis.[1]

Benefits of MHT

MHT remains the most effective treatment for vasomotor symptoms. In addition to the approved uses (VMS, GSM, bone protection), additional benefits have been reported for mood, sleep, joint pains, and quality of life.[5,6] Twenty years of follow-up after the WHI study provides reassuring evidence for cardiovascular safety.[10]

It is important to inform patients that while MHT can be effective for a number of symptoms, it is not the anti-aging solution they may be seeking. Evidence suggests a "window of opportunity" for cardio-protection when initiating MHT in healthy younger women at low baseline cardiovascular risk. However, guidelines do not support cardiovascular prevention as an indication for MHT.[1,5,6] MHT should also not be prescribed to prevent cognitive decline or dementia and initiating MHT after age 65 may lead to an increased risk of dementia. Although MHT might indirectly help with perimenopausal brain fog, there is insufficient research to support its use solely for this purpose.[11]

Notwithstanding the above considerations, MHT should be prescribed for women

Hormonal Options for Vasomotor Symptoms

Perimenopause

If no contraception required:

1. E + P: cyclic regimen recommended*:
i.e., Estrogen daily + Progestogen Day 1-14

2. Progestogen alone:
e.g., Progesterone 100-300 mg qhs
-less effective for VMS but some sleep benefit

If contraception is required:

3. Estrogen + 52 mcg Levonorgestrol IUS (*off label*)
- Evidence for endometrial protection with the IUS

4. Low dose combined hormonal contraception

*late perimenopause, "off label" when used earlier[1]

Postmenopause

1. E + P: continuous preferred
i.e., daily Estrogen + Progestogen

2. ET (Estrogen alone): if patient has hysterectomy

3. Continuous regimens that don't require the addition of a Progestogen*
a) CEE/BZA
b) Tibolone

*some patients are sensitive to progestogenic side effects such as bloating, headaches, water retention, low mood or somnolence

Figure 3. Hormonal Options for Vasomotor Symptoms; *courtesy of Susan Goldstein, MD, CCFP, FCFP, MSCP*

Abbreviations: E: Estrogen; **P:** Progestogen **ET:** Estrogen Therapy; **VMS:** Vasomotor symptoms

experiencing early menopause and premature ovarian insufficiency. These women are at a heightened risk for bone loss, cardiovascular disease, dementia, and other morbidities, and should be treated up to the natural age of menopause unless there are contraindications. This cohort often requires higher doses of MHT.[5,6]

Risks of MHT

When initiated in women under age 60 or within 10 years of their last menstrual period, the primary risk of MHT is venous thromboembolism (VTE). The highest risk (relative risk,1.74) occurs within the first 1-2 years of treatment.[9] Patients can be reassured that in this cohort, there is no significant increase in the risk of cardiac events or stroke.

The risk of breast cancer is associated with the duration of MHT use, increasing after approximately 5 years of EPT use. This risk may differ based on formulation, dose, mode of delivery, and the presence of and type of a progestogen. The WHI study documented a rare increase in breast cancer risk (<1/1000). While this study reported an increased incidence of breast cancer with the daily use of CEE 0.625 mg + medroxyprogesterone acetate (MPA) 2.5 mg, no increase in breast cancer mortality was observed.[10] This risk is comparable to the increased risk of breast cancer conferred by obesity or alcohol consumption. In contrast, for women using CEE alone, there was a reduction in breast cancer incidence (hazard ratio, 0.78) that persisted after the study ended.[12]

When breast risk is a concern (i.e., positive family history, dense breasts, breast pain) consider the following options which are less stimulating to the breast compared to a standard EPT containing a synthetic progestin. In order of preference these would be: The TSEC (CEE/BZA) followed by the STEAR (Tibolone), followed by EPT containing micronized progestogen.

Duration of Treatment

Vasomotor symptoms last a median of 7.4 years, and in some patients they may persist for 10 years or more. Up to 40% of women will continue to experience vasomotor symptoms into their 60's and 10-15% into their 70's.[1] As such, the duration of treatment should not be fixed, but rather individualized, with a periodic reassessment of indications, patient profile, and risks.

The evidence supports the safe continuation of MHT beyond 65 years when indicated.[13] As women age, switching to transdermal estrogen at the lowest effective dose is advised to help manage the increased cardiovascular risks associated with aging.

Conclusion

As healthcare providers, we need not fear prescribing MHT. Newer tools and research support us in providing a personalized menopause management plan for women with bothersome symptoms, taking into consideration the latest safety information on the multiple treatment options at our disposal.

Keep in mind that menopause represents a time when healthcare risks are evolving. Therefore, it is an important time to remind women about lifestyle changes they can make to optimize their health into the post menopause period of their lives.

Financial Disclosures

S.G.: Advisory boards: Astellas, Bayer, Eisai, Knight; **Unrestricted educational grant:** Canadian Menopause Society (CMS); **Speaker's fees:** Astellas, CMS, Bayer, Humber River Hospital, OCFP

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doi.org/10.58931/cpct.2025.3141

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The Global Health Compass: Steering Your Patients Through Travel Risks and Pandemic Concerns

Michael Boivin, Bsc, Phm, RPH, CDE, CBE

Canadian Travel and Primary Care

Canadian-resident trips abroad continued to increase in 2024 and surpassed their 2023 levels by 10.0%.[1] Overseas trips by Canadians increased by 30.9% from 2023 and now exceed pre-pandemic numbers.[1]

Although international travellers are an important group for the world economy, they are at increased risk of exposure to infectious diseases while they are outside their home country and may possibly spread these diseases from one country to another.[2] SARS-CoV-2, Ebola, Zika, and antimicrobial resistant pathogens are examples of health threats whose spread has been facilitated by international travellers.[2] Climate change is also impacting infectious disease risk.[3] Rising temperatures are expanding the regions where vector-borne diseases (e.g., dengue, malaria, Chikungunya, Zika) can thrive, as well as increasing the risk of zoonotic (e.g., Avian influenza) and waterborne diseases (e.g., *Vibrio, E. coli*).[3]

As more Canadians travel, clinicians play a critical role in making travel recommendations. This article will focus on simple recommendations that can be made to reduce travel risks and highlight potential future pandemic concerns.

Five Travel Strategies You Can Make Tomorrow

With the increasing risks for Canadian travellers, primary care clinicians play a crucial role in reducing their patients' risks. To optimize travel health in primary care, a variety of strategies can be implemented in practice, such as:

1. Basic pretravel consultation
2. Basic recommendations for every traveller
3. Primary care travel vaccinations
4. Protection from vector-borne diseases
5. Assessing travel advisories and pandemic preparedness

1. Basic Pretravel Consultation

A pretravel consultation is a dedicated session to prepare travellers for health concerns that may arise during their trip.[4] During a travel health consultation, the clinician determines the risk based on destination, accommodations, activities, and underlying health conditions.[4] Given that a full pretravel consultation can take some time to complete, it may not be required for people

who are travelling to popular resort destinations such as the Caribbean or Mexico.

Primary care clinicians can quickly assess travel-related risks, by asking 4 questions and using their knowledge of their patient's health. These questions include:[4]

1. Where are you planning to travel?
2. What are you planning to do while there?
3. What type of accommodations will you have?
4. Have you ever received any travel vaccines?

The goal is to identify any red flags that may require further discussion. Travelling to destinations such as Africa or South Asia carries a much higher risk compared to standard resort destinations. Participating in more adventurous activities and staying in lower quality accommodations also carries a higher overall travel risk.

- **All travel carries some level of risk.[4] If the traveller has poor health, a complicated travel itinerary or has planned activities that dramatically increase the risk, consider referral to a travel clinic.**

2. Basic Recommendations for Every Traveller

Clinicians can offer recommendations to help reduce the risk for every international traveller **(Table 1)**.

Recommendation	Discussion
Recommend that they pack a travel health kit	• Designed to provide the supplies required to prevent illness, as well as handle minor injuries and illnesses • These kits normally consist of:[5] o Basic first-aid supplies o Medications such as hydrocortisone, loperamide, dimenhydrinate, electrolyte pouches, antibacterial ointment, over-the-counter analgesics, gastrointestinal medications, and sunscreen o Any prescription medication. It is important to remind travellers to bring extra medication in case of travel delays and to ensure that all medications are in labelled containers for customs • Detailed travel health kit lists can be downloaded from: o Travel health kit (https://travel.gc.ca/travelling/health-safety/kit) o Travel Health Kits (https://www.cdc.gov/yellow-book/hcp/preparing-international-travelers/travel-health-kits.html)
Ensure they have travel insurance	• Severe illness or injury abroad could cause a financial burden[6] • Many travellers assume their home health insurance will cover any health expenses while travelling • Remind travellers to check if they have travel insurance through their workplace, and if not, encourage them to purchase a policy that supports their travel itinerary
Advise caution about what they eat or drink	• Food-borne illnesses are a common source of illness among travellers • Basic recommendations can help to reduce the risk. These include: o **Food:**[7] • Avoid raw or undercooked food (e.g., meat, fish, shellfish) • Avoid consuming salads, uncooked vegetables, raw unpeeled fruit, unpasteurized fruit juices, or dairy • Avoid street vendors • Quick recommendation: Hot food is generally safe whereas colder food may be contaminated o **Beverages:**[7] • Tap water might be unsafe for drinking, preparing food and beverages, making ice, cooking, and brushing teeth • When served in unopened, factory-sealed containers, carbonated beverages, commercially prepared fruit drinks, water, alcoholic beverages, and pasteurized drinks are generally safe • **Quick recommendation**: Hot drinks are generally safe, whereas iced drinks may not be

Recommendation	Discussion
Basic security and accident prevention	• Accidents and injuries pose a major risk • Inform travellers that automobile accidents and water injuries are a major source of health-related issues[8] • Travellers should be informed about safety and security while travelling, as the risks can vary based on the country, location, and accommodations[9] • To learn more about the risks of injury and safety while travelling, consider reviewing: o Statement on Risk of Injury and Travel (https://publications.gc.ca/collections/collection_2010/aspc-phac/HP3-2-36-13.pdf) o Injury & Trauma (https://www.cdc.gov/yellow-book/hcp/environmental-hazards-risks/injury-and-death-during-travel.html) o Safety & Security Overseas (https://www.cdc.gov/yellow-book/hcp/environmental-hazards-risks/safety-and-security-overseas.html)

Table 1. Basic travel recommendations; *courtesy of Michael Boivin, Bsc, Phm, RPH, CDE, CBE*

3. Travel Vaccination Primary Care

Several travel vaccines can be administered in primary care. The vaccine recommendations can vary based on the location of travel, planned activities in the country, accommodations, and the time of travel. **Table 2** provides a list of common travel-related vaccines for consideration in primary care.

Disease and Transmission	Symptoms and complications	Populations to consider for vaccination	Vaccine preparation and normal schedule	Comments
Chikungunya virus[11] **Transmission:** Vector-borne from *Aedes* mosquito	Up to 28% of individuals are asymptomatic Acute symptoms include high fever and joint pain, conjunctivitis, rash, myalgia, nausea, vomiting 5% to 80% of individuals develop persistent joint pain and prolonged fatigue lasting for months or years	Travellers to endemic or epidemic regions Adventure travellers or those travelling long-term Consider vaccination for travellers to areas at risk for Chikungunya. The CDC has an updated list here	For those ≥18 years, administer 1 dose of a live attenuated vaccine intramuscularly	Occurs in tropical and subtropical regions Outbreaks do occur, increasing transmission risk The need for a booster has not been established[12]
Hepatitis A virus[13,14] **Transmission:** Fecal-oral transmission through contaminated food or water	Symptoms can range from mild illness to severe disease Clinical manifestations include abrupt onset of fever, malaise, anorexia, nausea, and abdominal discomfort, followed by jaundice	Travellers who are not immune and are visiting developing countries	For those ≥6 months of age, administer 2 doses of inactivated vaccine intramuscularly 6-36 months apart	2-doses provide long-term protection (>20 years) Available in combination with the hepatitis B vaccine

Disease and Transmission	Symptoms and complications	Populations to consider for vaccination	Vaccine preparation and normal schedule	Comments
Hepatitis B virus[15,16] **Transmission:** Person-to-person with infected body fluids or skin-penetrating procedures (e.g., acupuncture, piercing, tattooing)	Symptoms can include abdominal pain, anorexia, fatigue, fever, jaundice, joint pain, malaise, nausea, vomiting, and dark urine. The overall case-fatality ratio of acute hepatitis B is approximately 1% Chronic infection occurs in <5% of individuals >5 years of age	Travellers who are not immune should be immunized, as Hepatitis B virus is endemic worldwide	For adults ≥19 years, administer 3 doses of inactivated vaccine intramuscularly (days 0, 30, 180)	Long-term protection is provided, and booster doses are not recommended for immunoc-ompetent individuals A rapid schedule is available Available in combination with the hepatitis A vaccine
Japanese encephalitis virus[17,18] **Transmission:** Vector-borne from *Culex* mosquito	99% of individuals are asymptomatic Symptomatic individuals can develop encephalitis, mental health changes, neurological deficits, and parkinsonian syndrome The case-fatality is 20%-30%, but 30%-50% of survivors have neurologic, cognitive or psychiatric sequelae	Travellers visiting rural epidemic areas, especially for trips >30 days People who have low risk tolerance	For adults aged 18-65 years, administer 2 doses of inactivated vaccine intramuscularly 28 days apart	Endemic in Asia and parts of the western Pacific Risk is low for most travellers Symptomatic cases can have severe consequences No antiviral treatments are available An accelerated schedule administered on days 0 and 7 is available
Meningococcal disease[19,20] **Transmission:** Direct person-to-person through infected droplets	50% of cases present as meningitis with a case-fatality rate of 10%-15% Approximately 30% of individuals develop meningococcal sepsis 10% to 20% of survivors have long-term sequelae	Travellers to areas where vaccination is recommended (e.g., the meningitis belt of Africa) or required (e.g., Hajj pilgrimage)	A variety of quadrivalent inactivated vaccine (ACWY) formulations are commonly used for travellers. They are administered as a single intramuscular dose 7-10 days before travel Meningococcal B vaccines are also available	Re-vaccination is recommended every 3 to 5 years for those at continued risk

Disease and Transmission	Symptoms and complications	Populations to consider for vaccination	Vaccine preparation and normal schedule	Comments
Rabies virus[21] **Transmission:** Virus presents in saliva and normally occurs through the bite of an infected animal	Pain and paresthesia occur at the site of exposure Swallowing and muscle spasms can be stimulated by the sight, sound, or perception of water (hydrophobia). Delirium and convulsions can develop, quickly followed by coma and death	Travellers at risk of direct contact with infected animals, those with considerable exposure to domestic animals, or those spending substantial time in high-risk rural areas	The inactivated vaccine is administered intramuscularly in 3 doses (days 0, 7, 21-28)	Endemic worldwide except Antarctica 100% fatality rate Vaccination simplifies management if an infected animal bites the traveller Educate travellers on the necessary protocol if they are bitten, as they will require additional doses of the vaccine
Typhoid fever[22,23] **Transmission:** Fecal-oral transmission through contaminated food or water	Fatigue, fever, anorexia, headache, and malaise are nearly universal symptoms, along with abdominal pain, constipation, or diarrhea Untreated case-fatality rate is 10%-30%	Travellers to low- and middle-income countries, especially South Asian communities Travellers visiting friends and relatives	For those ≥2 years of age, administer 1 dose of inactivated vaccine intramuscularly For those ≥5 years of age, administer 1 oral capsule on alternate days for a total of 4 capsules of vaccine, taken on an empty stomach	Endemic in Africa, Latin America, and Asia Administer an intramuscular booster every 3 years Administer an oral capsule booster every 7 years

- **Always assess the traveller for routine vaccines they may require (e.g., COVID-19, influenza, pneumococcal, respiratory syncytial virus [RSV]) to reduce their risk of illness while travelling.**

Table 2. Common travel-related vaccines for primary care[10]

on patient factors as well as local resistance patterns.[28] If a patient is travelling to a malaria-endemic area, primary care clinicians are encouraged to refer to travel health professionals to ensure the traveller is aware of the risk and to choose the most appropriate treatment option for the trip. The CDC in the US provides recommendations for chemoprophylaxis agents for different travel destinations. These can be accessed at:

- Malaria summary and medication review
- Malaria travel recommendations by country

Other vector-borne conditions include:

- Dengue virus
- Zika

All travellers should be encouraged to use an insect repellant to reduce their risk.[24] The two recommended insect repellants are DEET and icaridin (20%).[25] Icaridin is preferred for use in children.[25] Avoiding exposure through the use of long-sleeved clothing and bed nets can further reduce the risk for certain travellers.[25]

- **Sunscreen can be applied with insect repellants. Sunscreens should be applied first, followed by the insect repellant.[24]**

5. Assessing Travel Advisories and Pandemic Preparedness

The risk associated with international travel varies due to regional health or security issues. Consider checking for travel advisories prior to leaving. These advisories can be found at:

- Travel advice and advisories by destination (https://travel.gc.ca/travelling/advisories)

The COVID-19 pandemic has shown the global impact of the spread of infectious disease. International travel and a changing climate increase the risk of disease transmission between countries.[27]

At the time this article was developed, the risk associated with avian influenza (H5N1) was unknown. Outbreaks have been occurring in both domestic and wild birds with some transmission to other mammals and humans.[26] The risk for travellers remains low at this time, but this situation may change. For up-to-date recommendations, the Government of Canada has developed a website that includes current information:

- Avian influenza A (H5N1): For health professionals

What You Can Do in Practice Tomorrow

Canadians will continue to travel more frequently. There are infectious disease risks in many travel regions and potential pandemic pathogens could further increase this risk.

The recommendations in this article can help identify a traveller's risk and offer strategies to reduce them. Clinicians should consider discussing travel plans with their patients. By briefly discussing their trip, and offering recommendations, including vaccines, clinicians can help to ensure their patients are protected while travelling.

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Financial Disclosures

M.B.: Honoraria/speaker's fee: Teva, Pfizer, Novo Nordisk, mdBriefcase, Kenvue, Abbvie, Astra Zeneca, Boehringer Ingelheim, Moderna, Canopy, Valneva, Abbott Diabetes, GSK; **Advisory Boards or Speakers' Bureau:** Novo Nordisk, Emergent BioSolutions, Pfizer, Novavax, GSK, Bavarian Nordic, Valneva, Abbvie

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doi.org/10.58931/cpct.2025.3142

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Dr. Navdeep Tangri, MD, PhD, is working on a clinical research program that is also translational, focusing on the improvement of clinical decision making for patients with advanced chronic kidney disease. He developed and validated the Kidney Failure Risk Equation (KFRE) to predict the need for dialysis in patients with chronic kidney disease, and is currently engaged in multiple validation and implementation exercises to increase the uptake of the KFRE.

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Risk Prediction for Chronic Kidney Disease: Considerations for Primary Care

Navdeep Tangri, MD, PhD

Introduction

Chronic Kidney Disease (CKD) affects more than one in ten Canadians and is largely managed in primary care.[1] Diabetes is the leading cause of CKD, and primary care providers often manage the underlying causes and comorbid conditions related to kidney disease, as well as the adverse consequences of CKD itself.

It is important to recognize that CKD has a variable course. While most adults lose approximately 1 mL/min of kidney function every year after the age of 40, some patients lose kidney function rapidly, leading to hospitalizations due to heart failure and progression to kidney failure, whereas others remain stable for decades, requiring minimal additional intervention. Recent[2] advances in risk prediction for CKD allows all providers to accurately identify high risk individuals. These innovations enable the use of highly effective therapies that slow down, and in many cases, normalize the rate of kidney function loss, leading to potential lifetime risk reduction for kidney failure. **(Figure 1)**.

This review will cover key considerations in screening, risk stratification, and treatment of CKD in primary care, with an emphasis on tools that are readily available in clinical settings. We believe that a screen-triage-treat paradigm for CKD can lead to optimal outcomes for patients and health systems.

Screening

Mortality rates for kidney failure requiring dialysis exceed rates for Stage 3 colorectal cancer, yet there are no recommendations for universal CKD screening in Canada.[4] As such, current clinical guidelines recommend a case finding approach, which suggests screening with eGFR and albumiunuria (urine albumin to creatinine ratio) in certain groups at high risk of developing CKD.[5]

Guidelines from Diabetes Canada and global kidney disease guidelines strongly endorse screening individuals with diabetes for CKD with eGFR and albuminuria on an annual basis. Additional guidance recommends screening should be expanded to include adults with hypertension, cardiovascular disease, individuals with a strong family history (first degree relative with kidney failure), as well as high risk ethnic groups such as indigenous Canadians **(Figure 1)**.

In Canada, and in the United States, the rate

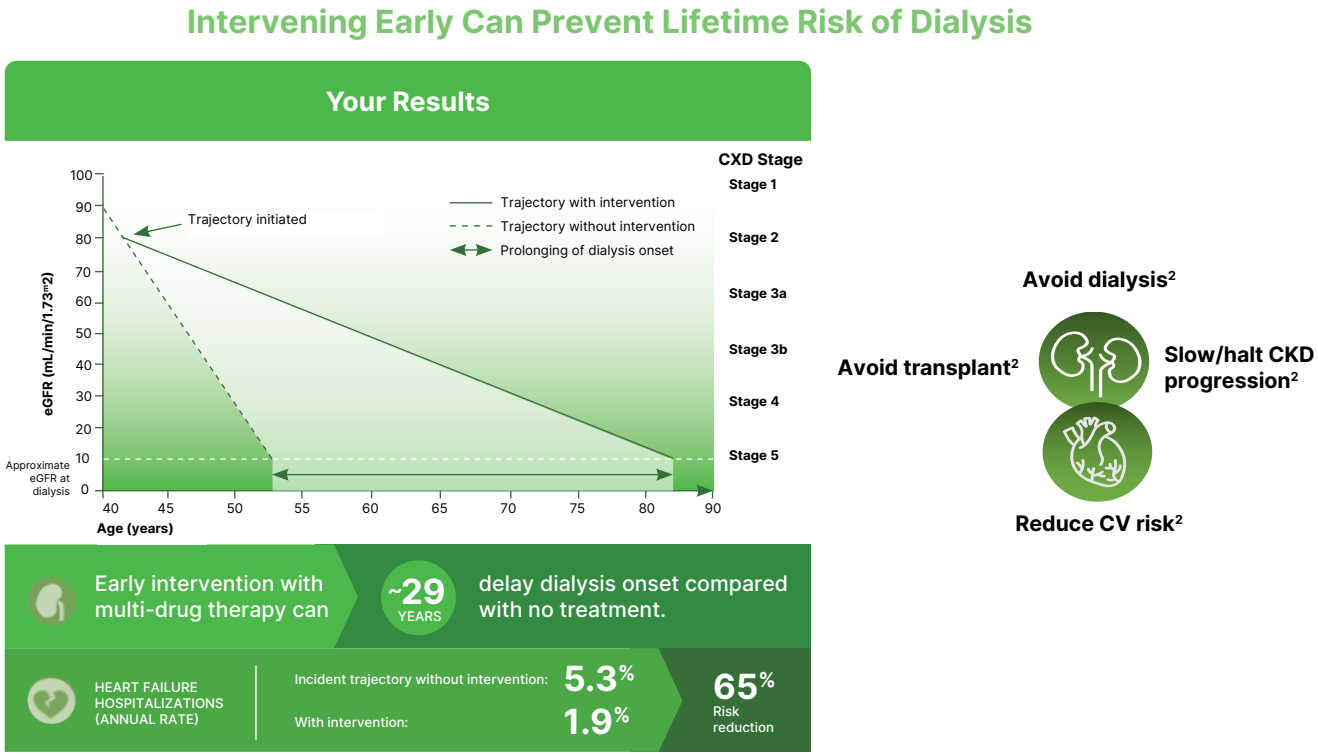

Figure 1. Benefits of early intervention in high risk patients with CKD (actearlyonkidney.com); *courtesy of Navdeep Tangri, MD, PhD*

of albuminuria testing, even among people with diabetes, remains below 50%, which suggests a major gap in implementing appropriate CKD screening.[6] We believe that automating processes, such as alerts in electronic medical records, and the addition of urine ACR into to routine annual bloodwork, can help close this gap in primary care.

Risk Stratification

It is now possible to estimate the risk of progression for all patients with CKD using routinely collected lab data. For patients in the later stages of disease (eGFR 15-60 ml/min), we developed the kidney failure risk equation (KFRE) to estimate the risk of dialysis or transplantation within the next 2-5 years.[7]

The KFRE was developed in patients from Ontario and originally validated in an independent sample of adults with CKD from British Columbia. Since the original publication in 2011, the KFRE has been validated in more than 30 countries involving 2 million individuals and has been used in more than 180 countries worldwide. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines and Diabetes Canada recommend it.[8]

The KFRE requires spot eGFR, urine ACR, age, and sex for calculation, without needing historical data or information on comorbid conditions or blood pressure. It can be automatically calculated in laboratory information systems and electronic medical records, and is included in all routine labs in Ontario, and in leading EMR software platforms, such as EPIC. Primary care providers can use the KFRE to determine the need for nephrology referrals (> 5 % risk in 5 years), as well as to counsel older adults who may have low risk CKD and do not need education or planning for dialysis.[9]

Risk Prediction for Earlier Stages of Disease

Awareness of CKD among both patients and physicians remains limited. As a result, most patients go undiagnosed and suboptimally treated until their eGFR falls below 45 mL/min, by which point more than half of kidney function is already lost. Furthermore,[10] the benefits of disease-modifying therapies for CKD progression are greatest when initiated earlier in the disease course, a stage when CKD goes unrecognized. To accurately identify patients at high risk of CKD progression at all stages of disease, we have

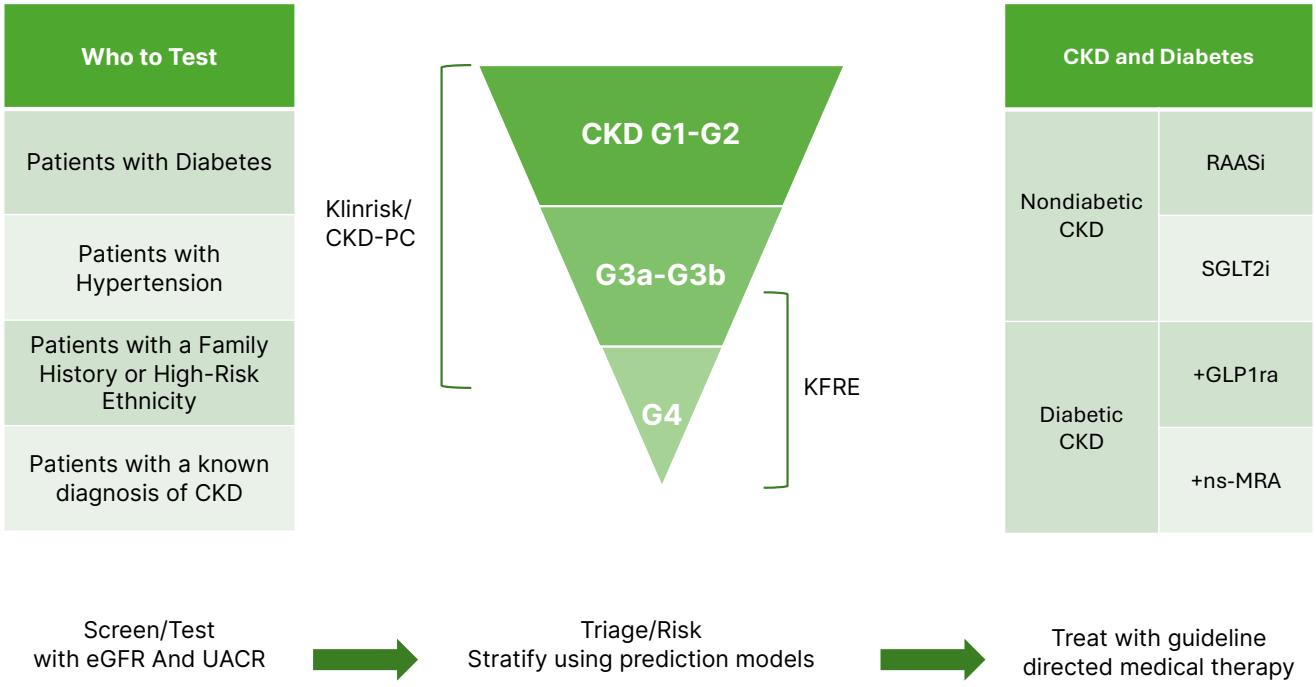

Figure 2. A screen, triage and treat paradigm for management of CKD in primary care; *courtesy of Navdeep Tangri, MD, PhD*

Abbreviations: CKD: chronic kidney disease; **GLP-1 RAs:** GLP-1 receptor agonists; **KFRE:** kidney failure risk equation; **ns-MRA:** Non-steroidal mineralocorticoid receptor antagonists; **RAASi:** Renin-angiotensin-aldosterone system inhibitors; **SGLT2i:** Sodium-Glucose Transport Protein 2 Inhibitors

developed highly accurate models that can be used in clinical care.

The Klinrisk models, which are machine learning based, use data from routine CBC, metabolic panels and urine ACR to predict the likelihood of CKD progression in the next 5 years. CKD progression is defined as a loss of 40% or more in kidney function, an outcome which has been validated as an appropriate surrogate for dialysis/kidney failure by regulatory bodies and is appropriate at any level of eGFR.[11]

These models were developed in Manitoba and Alberta and have subsequently been validated in clinical trial populations, as well as more than 6 million adults from Canada and the United States, with a wide range of age, underlying disease, and socioeconomic status. In the overall population, and in these subpopulations, the models have consistently showed excellent discrimination (AUC > 0.8) as well as good calibration/agreement between the predicted risk of event and the actual observed risk.[12-14]

Importantly, these models fill a key gap in care – by ensuring the appropriate blood and urine tests are ordered (CBC, metabolic panel, urine ACR), the interpretation is accurate (low, intermediate or high-risk CKD), and by connecting the tests to relevant clinical practice guidelines. The combination of these three key processes results in meaningful improvements in quality of care, focused on the patients with the highest need. In Ontario, these models are available through Lifelabs Inc., a leading provider of laboratory services.

In addition to these laboratory-based models, we developed models that use routinely collected demographic data and comorbid conditions that are freely available as an online risk calculator. These models (available from CKD-PC Models) use 14 routinely available variables, and predict the same outcome of CKD progression with good discrimination (AUC 0.74-0.77) in patients with or without diabetes.[15]

Using the Klinrisk or the CKD-PC models, primary care providers can identify patients who have intermediate or high-risk CKD at the point of care and take appropriate actions. Today, these actions can include the prescription of highly effective therapies that both slow CKD progression and address the underlying comorbid conditions **(Figure 2)**.

How Do We Approach Treatment in The 4 Drug Era By Delivering Risk-based Care

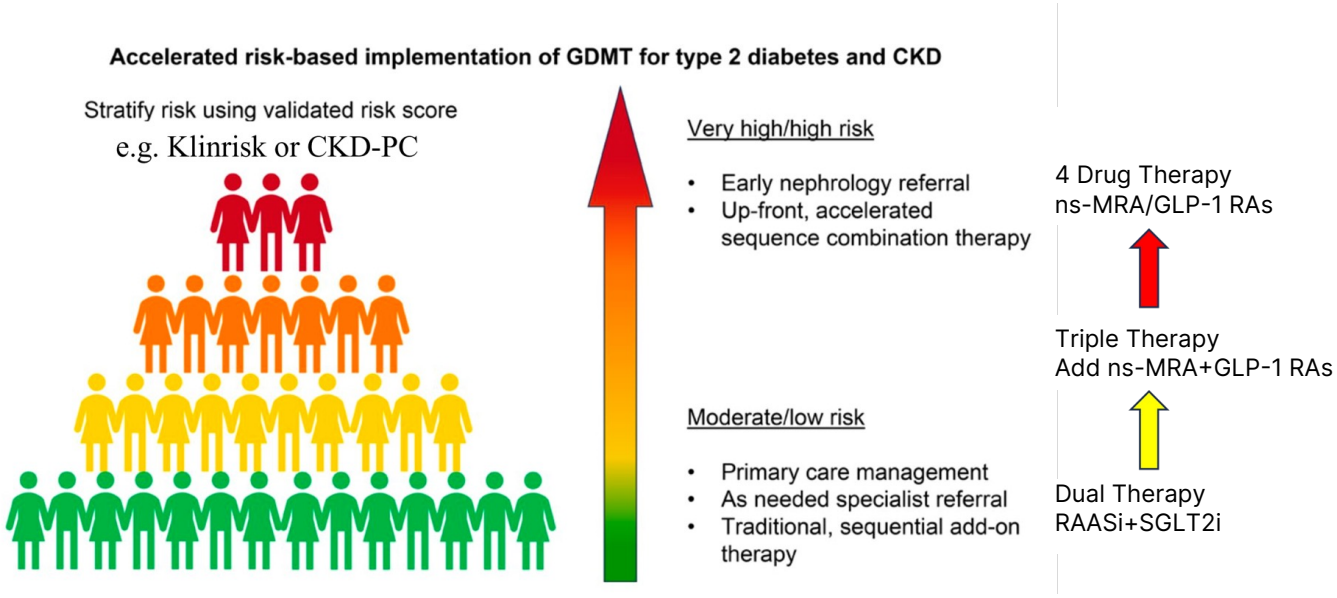

Figure 3. An approach to delivering risk based care; *Adapted from Neuen et al. Circulation 2024*

Abbreviations: CKD: chronic kidney disease; **GLP-1 RAs:** GLP-1 receptor agonists; **ns-MRA:** Non-steroidal mineralocorticoid receptor antagonists; **RAASi:** Renin-angiotensin-aldosterone system inhibitors; **SGLT2i:** Sodium-Glucose Transport Protein 2 Inhibitors

A Risk Based Treatment Paradigm

We now have access to four highly effective classes of treatment that slow CKD progression in patients with diabetes **(Figure 1)**. Trils of Non-steroidal mineralocorticoid receptor antagonists (ns-MRAs) and GLP-1 receptor agonists (GLP-1 RAs) for non-diabetic CKD patients are ongoing and will report findings in the next 12-24 months.

Primary care providers are very familiar with prescribing both Renin-angiotensin-aldosterone system inhibitors (RAASi) and Sodium-Glucose Transport Protein 2 Inhibitors (SGLT2i), but rates of SGLT2i use, particularly in those with non-diabetic kidney disease remain low. Our work, and work by others shows that the benefits of SGLT2i are independent of diabetes status, and that patients at all levels of risk have an improvement in their rate of kidney function decline with SGLT2i use. As such, we recommend that RAASi and SGLT2i be considered foundational therapy for all patients with CKD.

For patients with intermediate and high-risk disease, we believe that a risk-based care paradigm should be applied and can most effectively balance the benefits of additional therapy (GLP-1 RAs or ns-MRA) vs the risks of side effects, polypharmacy and costs. **(Figure 3)** For intermediate risk patients, the choice of ns-MRA vs GLP-1 RAs should be made on patient preferences regarding injection, body mass index, glyemic control and serum potassium.

For high risk patients, there is likely to be benefit for both cardiovascular and kidney events with use of GLP-1 RAs and ns-MRA. These patients typically lose ~ 3 mL/min/year even with RAASi and SGLT2i therapy, and additional treatment can further reduce albuminuria and risk, and potentially lower the risk of all cause death. Communication of risk including the use of visual aids **(Figure 3)** can help engage the patients in shared decision making and thereby improve initiation and reduce discontinuation of these highly effective therapies.

It is important to note that no data to date demonstrates any interactions between these therapies (SGLT2i, GLP-1 RAs, ns-MRA) with respect to safety and efficacy and physicians should assume that these treatments, with their independent mechanisms of action have additive effects on slowing the progression of disease. Nonetheless, the benefit is the largest in the patients at the highest risk of progression, further supporting the intensification of treatment in high risk individuals.

Summary

Of the more than 4 million Canadians with CKD, less than 500,000 receive care from a nephrologist. We believe that accurate and usable risk prediction tools like the KFRE and the Klinrisk model can enable primary care providers to deliver the same quality of care as a kidney specialist for the vast majority of patients with, or at risk for, CKD.

In addition, risk prediction tools can help engage the patient in their care journey, improve awareness and shared decision making, and also provide valuable reassurance to patients and families who may perceive CKD to be equivalent to kidney failure. Ultimately, a risk-based care paradigm will lead to more personalized care for this vulnerable population.

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Financial Disclosures

Consultancy: Prokidney Corp., PulseData Inc, Mesentech Inc., Marizyme, Roche; **Ownership Interest:** Prokidney Corp., PulseData Inc, Mesentech Inc., Marizyme, Klinrisk, Quanta; **Research Funding:** Astra Zeneca Inc., Tricida Inc, Janssen, Otsuka, BI-Lilly, Bayer, Roche; **Honoraria:** Astra Zeneca Inc., BI-Lilly, Bayer, Renibus; **Patents or Royalties:** Mar- izyme, Klinrisk; **Other Interests or Relationships:** National Kidney Foundation

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Canadian Primary Care Today
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Canadian Primary Care Today is published three times per year in English and French.
(ISSN 2817-4178) under the terms of the

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