INESSS
LE SAVOIR PREND FORME

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INHALED MEDICATIONS

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

GENERAL INFORMATION

- Chronic obstructive pulmonary disease (COPD) is characterized by expiratory airflow limitation, which causes persistent, progressive respiratory symptoms.
- COPD often encompasses the phenotypes of chronic bronchitis and emphysema when associated with bronchial obstruction and is generally observed in individuals 40 years of age and older.
- Comprehensive management (Appendix A) involves the individual's participation in their care, the use of pharmacological and nonpharmacological measures, and interprofessional collaboration.

RISK FACTORS

- **Current or past tobacco smoking (main risk factor)**
- Current or past regular inhalation of any type of smoke (e.g., cannabis, cigarillos or chicha)
- Current or past prolonged exposure to particles or gases: second-hand tobacco smoke, cooking or heating biomass fuels, and occupational dusts and chemicals
- Factors in medical history:
  - Recurrent lower respiratory tract infection
  - History of asthma, childhood respiratory infection, or tuberculosis
  - Documented developmental lung abnormalities: preterm birth/low birth weight
  - Family history of COPD or the presence of an identified genetic disease (e.g., alpha-1 antitrypsin deficiency)

CLINICAL PRESENTATION

MAIN SYMPTOMS SUGGESTIVE OF COPD	OTHER POSSIBLE SYMPTOMS AND SIGNS
▸ **Dyspnea** (the most common symptom): - that seems inappropriate during the activities of daily living or that is disproportionate or accentuated with exertion - that persists and progresses over time ▸ **Chronic cough*:** - constant or intermittent - especially in current or former smokers ▸ **Chronic bronchial secretions/expectorations*:** - generally associated with the presence of chronic bronchitis ** The chronicity of these symptoms is generally defined as their being regular and failing to resolve.*	*List not exhaustive* ▸ Symptoms - Feeling of tightness in the chest - Wheezing - Fatigue, low energy level and diminished exercise capacity ▸ Vital signs - Elevated respiratory rate - Diminished oxygen saturation ▸ Signs on visual inspection - Reclined position to facilitate breathing - Pursed lip breathing - Use of accessory muscles of respiration ▸ Signs on auscultation - Decreased vesicular murmur and heart sounds - Crackles or bronchial wheezing

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DIAGNOSTIC APPROACH

- **Failure to recognize COPD is the cause of its underdiagnosis.** Dyspnea may be masked by adjusting the activities of daily living.
- **To make the right diagnosis, additional investigations are usually required.** The symptoms of and risk factors for COPD are common to other clinical conditions.

DIAGNOSTIC CRITERIA

The possibility of COPD should be considered in:

- ✓ The presence of at least 1 of the main symptoms suggestive of COPD AND
- ✓ The presence of at least 1 of the COPD risk factors

Spirometry (diagnostic test)

Forced expiratory volume in one second (FEV_1) over forced vital capacity (FVC), determined by spirometry, is the best way to establish the presence of bronchial obstruction.

- **COPD is confirmed if the absolute value of the post-bronchodilator FEV_1/FVC ratio is less than 0.7.**

❗ An acute exacerbation may be the first clinical manifestation of undiagnosed COPD. If one occurs, spirometry should be performed later during a period of clinical stability.

DIFFERENTIAL AND CONCURRENT DIAGNOSES

- If the clinical picture is consistent with COPD, **consider the following additional investigations:**
  - A complete blood count with a white blood cell differential (especially to know what the blood eosinophil count is)
  - A chest x-ray, as clinically indicated
  - An electrocardiogram, as clinically indicated
- Other tests specific to cardiac involvement (echocardiography, BNP/NT-proBNP) could be considered.

THE MOST COMMON DIFFERENTIAL AND CONCURRENT DIAGNOSES ARE:		
▸ Anemia	▸ Lung cancer	▸ Interstitial lung disease
▸ Asthma	▸ Heart failure	
▸ Bronchiectasis	▸ Atherosclerotic cardiovascular disease	

Non-exhaustive list in alphabetical order. Depending on clinical judgment, other differential and concurrent diagnoses could be considered.

CONSULTATION WITH A SPECIALIST IN PNEUMOLOGY

Consider consulting a respirologist or an experienced colleague in the following situations:

- ✓ Respiratory symptoms disproportionate to the degree of bronchial obstruction
- ✓ An uncertain diagnosis or differential diagnoses to be ruled out
- ✓ The presence of unusual symptoms, such as hemoptysis, to rule out malignancy or pulmonary embolism
- ✓ Circumstances and symptoms suggestive of alpha-1 antitrypsin deficiency (e.g., emphysema or COPD at a young age, a diagnosis of COPD before age 65 and fewer than 20 pack-years of smoking, or unexplained liver disease)
- ✓ A diagnosis of COPD **AND**:
  - Suspicion of concurrent asthma: strong possibility if the post-bronchodilator change in FEV_1 is greater than 400 ml
  - Under 40 years of age with limited history of smoking
  - Exposure to occupational particles and no history of smoke exposure
  - Advanced stage requiring specialized care

CLINICAL AND FUNCTIONAL EVALUATION

SEVERITY OF BRONCHIAL OBSTRUCTION

The post-bronchodilator forced expiratory volume in one second (FEV_1) is useful for determining the severity of bronchial obstruction following diagnosis and for monitoring the progression of COPD in the event of a rapid clinical deterioration.

COPD SEVERITY – POST-BRONCHODILATOR FEV_1 ACCORDING TO PREDICTED VALUE			
Mild	Moderate	Severe	Very severe
≥ 80%	≥ 50% and < 80%	≥ 30% and < 50%	< 30%

TYPE AND SEVERITY OF SYMPTOMS

Questions about the type of work the person does, their work environment and their home environment can help assess the symptoms.

Validated clinical tools are available for assessing the type and severity of COPD symptoms on a regular basis to guide or optimize treatment decision-making.

- The modified Medical Research Council (mMRC) scale [details in Appendix B)
  - is used to measure the level of dyspnea
- The COPD Assessment Test (CAT™)[1], a self-questionnaire:
  - focuses on symptom severity and quality of life

	SYMPTOM SEVERITY ACCORDING TO THE CLINICAL TOOLS CAT™ AND mMRC		
	Few or no symptoms	Significant presence of symptoms	Severe symptoms
mMRC	≤ 1	2	≥ 3
CAT^{MC}	< 10	≥ 10 and ≤ 20	> 20

RISK OF ACUTE EXACERBATIONS

Assessing the risk of acute exacerbations helps guide or optimize treatment decision-making.

The risk of acute exacerbations is high if, in the past year:

- 2 or more acute exacerbations required an oral corticosteroid and/or an antibiotic (i.e., ≥ 2 moderate exacerbations) OR
- 1 or more acute exacerbations required hospitalization (i.e., ≥ 1 severe exacerbations)

COMORBIDITIES

- Cardiac, pulmonary and mental health comorbidities that contribute to COPD symptoms are common, and managing them reduces COPD complications.
- COPD predisposes the individual to certain respiratory comorbidities and infections with a risk of complications.

BLOOD EOSINOPHIL COUNT

The blood eosinophil count (EOS), measured when COPD is clinically stable (4 to 6 weeks or longer without an acute exacerbation) and without the use of oral corticosteroids, helps determine:

- The advisability of **adding** an inhaled corticosteroid (ICS), combined with long-acting bronchodilators, to reduce the frequency of acute exacerbations
  - EOS less than 100 cells/µl predicts little or no response
  - EOS between 100 and 300 cells/µl predicts a possible response
  - EOS of 300 or more cells/µl predicts a favourable response
- The risk of recurrence of acute exacerbations with ICS **withdrawal**
  - EOS of 300 or more cells/µl predicts a risk of recurrence of acute exacerbations

SPUTUM MICROBIOLOGY

- Sputum microbiology is clinically relevant only in patients with advanced COPD who have recurrent acute exacerbations, for better planning acute-phase antibiotic therapy. Refer to the guide Acute exacerbation of COPD (AECOPD).

1. CAT™ is a registered trademark of the GlaxoSmithKline (GSK) Inc. group of companies, which supported a multidisciplinary group of international COPD experts in the development of the test for evaluating this disease. All rights reserved.

TREATMENT PRINCIPLES

PHARMACOLOGICAL TREATMENTS

- A list of molecules and inhalation devices and their status with the Régie de l'assurance maladie du Québec is available here.
- Based on the symptom assessment, bronchodilators are indicated for the maintenance treatment of COPD. This can be supplemented with an ICS according to an approach guided by the risk of acute exacerbation.

SHORT-ACTING BRONCHODILATORS:

- Short-acting muscarinic antagonist [SAMA]
- Short-acting β_2-agonist [SABA]

- If necessary, to relieve acute dyspnea (considered as a rescue medication)

LONG-ACTING BRONCHODILATORS:

- Long-acting muscarinic antagonist [LAMA]
- – Long-acting β_2-agonist [LABA]

- To limit the symptoms of dyspnea, improve exercise tolerance and quality of life, and reduce the risk of acute exacerbation

INHALED CORTICOSTEROID (ICS)

- To decrease the frequency of acute exacerbations if the circumstances of its use are appropriate

Considerations for the use of an ICS in the treatment of COPD

✓ **An ICS must always be combined with long-acting bronchodilators.**

✓ The addition of an ICS is assessed primarily on the basis of the clinical profile and should take the following into account:
- a history of asthma or other comorbidities
- the risk of acute exacerbations (if high)
- episodes of pneumonia (if severe or frequent)

✓ Eosinophilia is a secondary decision criterion. A low EOS should not be a deterrent to trying an ICS if there is a high risk of acute exacerbation.

✓ Withdrawing an ICS in a person **at low risk** for acute exacerbation may be considered if:
- they experience severe or frequent episodes of pneumonia and the ICS is providing little benefit
- the initial indication was inappropriate (no history of acute exacerbation)

✓ Withdrawing an ICS is not recommended in the following situations:
- in persons who are or have been at high risk for acute exacerbation of COPD, because of the risk of increasing the frequency and severity of exacerbations. In such case, a discussion with a respirologist could be necessary.
- EOS ≥ 300 cells/µl, which suggests a significant risk of recurrence of acute exacerbations if an ICS is withdrawn.

CHOICE OF INHALATION DEVICE

The choice of inhalation device should be based on the treatment indications, the person's abilities and preferences, and the devices' characteristics.

Thus, the inhalation device should be chosen:

✓ **On the basis of the person's respiratory, cognitive and physical abilities**

Assessing the person's abilities is a must, as it is unlikely that there will be differences in clinical outcomes between the different inhalers available for the same class of molecule when used properly.

✓ **In partnership with the person**

A COPD patient is more likely to use their inhaler regularly and properly if they participated in selecting it and have confidence in it.

TREATMENT PRINCIPLES (CONTINUED)

- **The use of multiple inhalation devices in the same person should be avoided.** When a combination of molecules is necessary, preference should be given to a single device in which they are combined.
- The decision support tool Help in choosing an inhalation device contains useful information to guide the choice of an optimal device.

INITIAL PHARMACOLOGICAL TREATMENTS

Symptom severity	Risk of acute exacerbation not high	High risk of acute exacerbation
mMRC ≤ 1 or CAT™ < 10	Bronchodilator[1]	LAMA
mMRC = 2 or CAT™ ≥ 10 et ≤ 20	LAMA[2] or LABA	LAMA OR LABA + CSI if EOS ≥ 300 or history of asthma
mMRC ≥ 3 or CAT™ > 20	LAMA + LABA	LAMA + LABA OR LABA + CSI if EOS ≥ 300 or history of asthma

1. If the activities of daily living are compromised, a long-acting bronchodilator should be used.
2. A LAMA is preferable to a LABA for preventing acute exacerbations of COPD.

ADJUSTING PHARMACOLOGICAL TREATMENT

1) If the response to the current therapy is meeting the objectives:

→ continue with the same treatment

2) If the response to the current therapy is not meeting the objectives:

✓ check adherence to the treatment and to the nonpharmacological measures

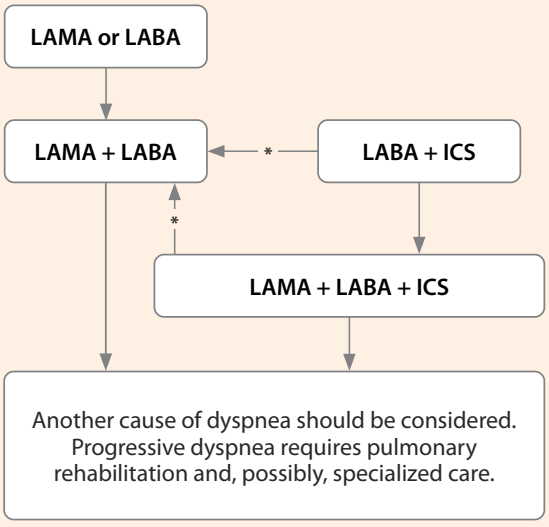
✓ check the inhalation technique

→ If the person is not using the proper technique, consider switching to another inhalation device

3) If the response is not meeting the objectives despite a treatment taken with appropriate manner:

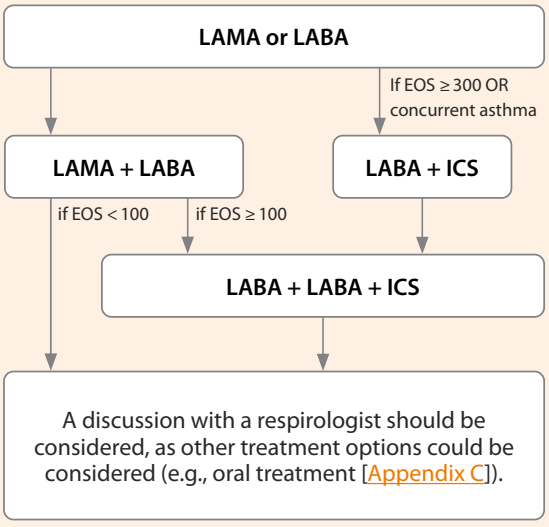
→ Consider escalating the pharmacological therapy according to the condition to be treated

DYSPNEA OR EXERCISE LIMITATION



HIGH RISK OF ACUTE EXACERBATION[1]

(to be considered predominantly when both conditions are present)



1. A high risk of acute exacerbation refers to two or more exacerbations that have required an oral corticosteroid and/or an antibiotic (i.e., ≥ 2 moderate exacerbations) in the past year OR one or more exacerbation that have required hospitalization (i.e., ≥ 1 severe exacerbation) in the past year.

* Withdrawing an ICS may be considered if its use carries risks that outweigh the benefits (see considerations for ICS use on the previous page). De-escalation is not recommended in anyone who has been or is at high risk for acute exacerbation.

THERAPEUTIC EDUCATION

For the purpose of self-management:

- Encourage the person to:
  - Initiate a smoking cessation process, if applicable, and offer support resources
  - Limit exposure to irritants, e.g. smoke, biomass and pollution
  - Get vaccinated to prevent respiratory infections: influenza, pneumococcus, SARS-CoV-2
  - Adopt healthy life habits: physical activity, diet and alcohol consumption
  - Learn about COPD and get answers to their questions about it
- Educate and target behavioural changes in daily life so that the person can:
  - Use inhalation devices properly
  - Improve the self-management of their symptoms: breathing and energy conservation techniques, stress management strategies, and recognizing aggravating factors of an acute exacerbation
  - Recognize a worsening of their health (acute exacerbation), understand their action plan and make the right decisions to reduce complications. The Quick reference guide helps support the person's self-management as an adjunct to their "written" action plan".

FOLLOW-UP

- Check adherence to the treatment, check the inhalation technique and assess tolerance and satisfaction with the treatment regularly and whenever a treatment change is being considered or has been made. Pay special attention to vulnerable individuals, who have a high frailty index or a major neurocognitive impairment.
  - Do a close follow-up (1 to 3 months after the start of treatment) to assess adherence and adverse effects
- The benefits of a pharmacological treatment should be assessed:
  - 3 to 6 months after the use of a long-acting bronchodilator is initiated
  - 6 to 12 months after starting a combination therapy that includes an ICS
- A spirometric assessment of the person's bronchial obstruction (FEV_1) should be considered only if there is a rapid clinical deterioration in their symptoms, a worsening of exercise limitation, or frequent or severe acute exacerbations.

REFERRAL TO MEDICAL SPECIALIST

- During the course of the disease, the person may be referred to a medical specialist in the following situations:
  - A rapid clinical deterioration with a decrease in their FEV_1 (if known)
  - Severe or recurrent acute exacerbations AND treatment failure or frequent lung infections
  - Severe COPD and disability requiring more intensive interventions
  - The appearance of signs of cor pulmonale (lower-limb edema)
  - The need for pulmonary rehabilitation (see Appendix A)
  - The need for an assessment for:
    - oxygen therapy, noninvasive ventilation or other surgical treatments
    - sleep disorders
    - more intensive management of comorbidities
  - The presence of symptoms and signs of:
    - hypoxemic or hypercapnic respiratory failure
    - pulmonary hypertension without daytime hypoxemia
  - Polycythemia
  - Refractory dyspnea / the need for comfort care, palliative care or end-of-life care
- An interprofessional geriatric assessment may be considered, depending on the clinical picture.

REFERENCES

The references can be found in the INESSS report associated with this optimal use guide.

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APPENDIX A

COMPREHENSIVE COPD MANAGEMENT

- The goals of comprehensive COPD management include:
  - Relieving the dyspnea and respiratory symptoms that are compromising daily activities;
  - Reducing the frequency and severity of acute exacerbations of COPD (AECOPD);
  - Slowing the progression of the disease;
  - Maintaining quality of life and autonomy;
  - Reducing the risk of morbidity and mortality.
- Comprehensive COPD management includes pharmacological and nonpharmacological measures. The use of nonpharmacological measures is necessary in order to optimize pharmacological treatment.
- A "written" action plan should be drawn up jointly with the person to guide them in recognizing when their symptoms change and in knowing what measures to take. The action plan should be accompanied by adequate self-management training and a follow-up with a health professional, and be updated at least every two years, or more frequently, depending on the person's situation.

COMPREHENSIVE COPD MANAGEMENT	
Intervention	Indication
• Smoking cessation • Cessation of exposure to irritants • Vaccination (influenza, pneumococcus, SARS-CoV-2) • Education • Adoption of healthy life habits: physical activity, diet, alcohol consumption, sleep, stress management	At any time once COPD is diagnosed ✓ To reduce the risk factors that worsen COPD (including AECOPD prevention)
• Short-acting bronchodilators	As needed ✓ To relieve acute dyspnea
• Long-acting bronchodilators	At any time ✓ To limit the symptoms of dyspnea, improve exercise tolerance, improve quality of life and reduce the risk of acute exacerbation
• Inhaled corticosteroids (ICS)	Used in combination with long-acting bronchodilators ✓ To reduce the frequency of acute exacerbations if the circumstances of their use are appropriate
• Pulmonary rehabilitation*	If symptoms persist or functional limitation and a decline in quality of life despite appropriate pharmacological and nonpharmacological management ✓ To improve exercise tolerance and health status and to prevent hospitalization
• Oral treatments* - Azithromycin (macrolide) - Roflumilast[1] (selective phosphodiesterase-4 inhibitor) - N-acetylcysteine (mucolytic agent)	When there is a high risk of AECOPD despite appropriate therapy with a long-acting bronchodilator with or without an ICS, as directed ✓ To prevent AECOPD
• Airway clearance technique: - Especially oscillatory positive expiratory pressure devices (e.g., Aerobika™)	In the presence of sputum, usually if concurrent chronic bronchitis or bronchiectasis ✓ To clear the airways and reduce the frequency of AECOPD
• Noninvasive home ventilation*	If stable COPD and chronic severe hypercapnia ($PaCO_2 \geq 52$ mm Hg)
• Oxygen therapy*	If chronic severe hypoxemia – resting $PaO_2 \leq 55$ mm Hg or ≤ 59 mm Hg in the presence of cor pulmonale or polycythemia
• Surgery*	If the patient is a candidate, different surgeries may possibly be appropriate, depending on lung volume, emphysema bubble size, or COPD severity
• Comfort or palliative care*	In the presence of refractory dyspnea ✓ To reduce certain symptoms and provide comfort

1. Uncovered by Quebec's public drug insurance plan.

* These interventions could require referring the person to a medical specialist or a specialized center.

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APPENDIX B

MODIFIED MEDICAL RESEARCH COUNCIL (mMRC) SCALE FOR THE ASSESSMENT OF DYSPNEA

- The mMRC scale assesses dyspnea severity by grading breathlessness on a scale of scores ranging from 0 to 4.

mMRC	
Score	Description
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of my age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing/undressing

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APPENDIX C

ORAL TREATMENTS

- In certain circumstances, oral therapies, concurrently with optimal inhaled therapy and an assessment of the potential wellness associated with a targeted therapy, may be considered when there is a high risk of acute exacerbation.

ORAL TREATMENTS			
	Indication	Precautions	Follow-up
Azithromycin (macrolide)	To reduce the frequency of exacerbations, preferably in former smokers who are at high risk	Risk of adverse effects: auditory, cardiac, antimicrobial resistance	Safety monitoring should be done for the first few weeks
Roflumilast[1] (selective phosphodiesterase-4 inhibitor)	To reduce the frequency of exacerbations, more specifically, when the FEV_1 is < 50% and in the presence of chronic bronchitis*	It is not recommended if the body mass index is low. Risk of rather frequent adverse effects: gastrointestinal intolerance, weight loss	Should be discontinued if adverse effects persist beyond 4 to 8 weeks after the start of treatment
N-acetylcysteine (mucolytic agent)	To reduce the frequency of exacerbations in certain selected individuals with large amounts of secretions or purulence	Risk of gastrointestinal adverse effects	Should be discontinued after 3 to 6 months if no benefit is observed

1. Uncovered by Quebec's public drug insurance plan.

* Cough and secretions present for at least 3 months over 2 consecutive years.

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