MANAGEMENT OF REFRACTORY COPD

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مدينة اللاذقية

INTRODUCTION

- COPD is a leading cause of death among adults, both in the United States and worldwide

INTRODUCTION

- COPD is a common condition with **high morbidity and mortality,** affecting males and females equally.

- It is estimated that approximately **10 % of individuals aged 40 years or older have COPD**, the prevalence varies between countries and increases with age.

For most patients with **less severe** **COPD, symptoms and exacerbations** can be controlled with interventions such as

- **inhaled medications** (bronchodilators and glucocorticoids).
- smoking **cessation**,
- **vaccinations** against influenza and pneumococcal infections,
- pulmonary **rehabilitation** ,

As the disease progresses,

- **COPD symptoms and exacerbations may be persistent despite these interventions.**

- While **refractory COPD has not been formally defined,**
- **severe, persistent symptoms or frequent exacerbations despite appropriate care.**

ASSESSMENT OF THE PATIENT WITH REFRACTORY COPD

- **Some** patients with COPD continue to have refractory **dyspnea and limitations to activity**. **Others** may have continued **cough and sputum** or

- **recurring exacerbations** despite therapy with LAMA, LABA and ICS therapies.

- In addition, these patients may also report **fatigue, weight loss, sleep disturbance, and anorexia.**

Symptoms reassessment

patients with **refractory COPD**

- benefit from a comprehensive **reassessment** of their symptoms and disease burden,

Evaluation of dyspnea

it is helpful in **refractory patients** to evaluate dyspnea and exercise tolerance **using**

validated instruments,

(mMRC) dyspnea scale

or

the COPD Assessment Test (CAT)

Calculator: COPD Assessment Test (CAT)

nput

	0	1	2	3	4	5	
I never cough	○	○	○	○	○	○	I cough all the time
I have no phlegm (mucus) in my chest at all	○	○	○	○	○	○	My chest is completely full of phlegm (mucus)
My chest does not feel tight at all	○	○	○	○	○	○	My chest feels very tight
When I walk up a hill or one flight of stairs, I am not breathless	○	○	○	○	○	○	When I walk up a hill or one flight of stairs, I am very breathless
I am not limited doing any activities at home	○	○	○	○	○	○	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	○	○	○	○	○	○	I am not at all confident leaving my home because of my lung condition
I sleep soundly	○	○	○	○	○	○	I don't sleep soundly because of my lung condition
I have lots of energy	○	○	○	○	○	○	I have no energy at all
	0	1	2	3	4	5	

- For each question, point values **range from 0 to 5 points.**
- **High CAT scores** are associated with high health impact.

Back

Calculator: Modified Medical Research Council (mMRC) scale for dyspnea

Input

Dyspnea scale

- ○ mMRC 0: Dyspneic on strenuous exercise
- ○ mMRC 1: Dyspneic on walking up a slight hill
- ○ mMRC 2: Dyspneic on walking level ground; must stop occasionally due to breathlessness
- ○ mMRC 3: Must stop for breathlessness after walking 100 yards [91 meters] or after a few minutes
- ○ mMRC 4: Cannot leave house; breathless on dressing/undressing

Result

Important: Inputs must be complete to perform calculation.

mMRC _____ **points**

To assess for **interval exacerbation** history,

- ask patients about periods of increased **dyspnea**, **sputum** volume, and sputum purulence, any treatments with **antibiotics** or **oral glucocorticoids** for respiratory symptoms.

- **COPD hospitalizations** mark severe exacerbations.

- also monitor **symptoms** commonly associated with COPD, such as **fatigue and sleep disturbance**.

- review **smoking history**, other **exposure history**,

- and **prior pulmonary function testing**

  to ensure that patients appropriately carry the diagnosis of COPD.

On **physical examination**,

- assess for **use** of the **accessory respiratory muscles** of the neck and shoulder girdle,
- **expiration** through pursed **lips**, **cyanosis**,
- asterixis due to severe hypercapnia,
- and **liver enlargement/tenderness** or
- **peripheral edema** due to right heart failure.

- A **falling** (BMI) is common in severe COPD,
- but a **rising BMI** may suggest **fluid retention** due to **right heart failure or comorbid heart failure**

- **decreased mental status** could reflect hypercapnia or hypoxemia.
- digital clubbing,
- **bibasilar fine crackles, and peripheral edema,**

might suggest a comorbidity or alternate diagnosis.

- reevaluation for **alternative diagnoses**, consideration for

- and assessment of ongoing **home exercise** is essential.

Optimizing inhaled therapies

- For patients who have **persistent symptoms** despite optimized inhaled therapies

  LAMA, LABA, and ensifentrine , ICS .

- it is critical to

  review patient **inhaler and/or nebulizer technique**, **adherence** to inhaler therapies,

- and any **adverse effects** the patient may be experiencing.

- This information may **prompt changes** in inhaled agents used, **device type**

  pressurized **metered dose inhaler** (pMDI)

  versus **dry powder inhaler** (DPI)

  versus **soft mist inhaler** (SMI) or

  nebulizer),
- or **dosing schedule** to address these concerns.

Adherence

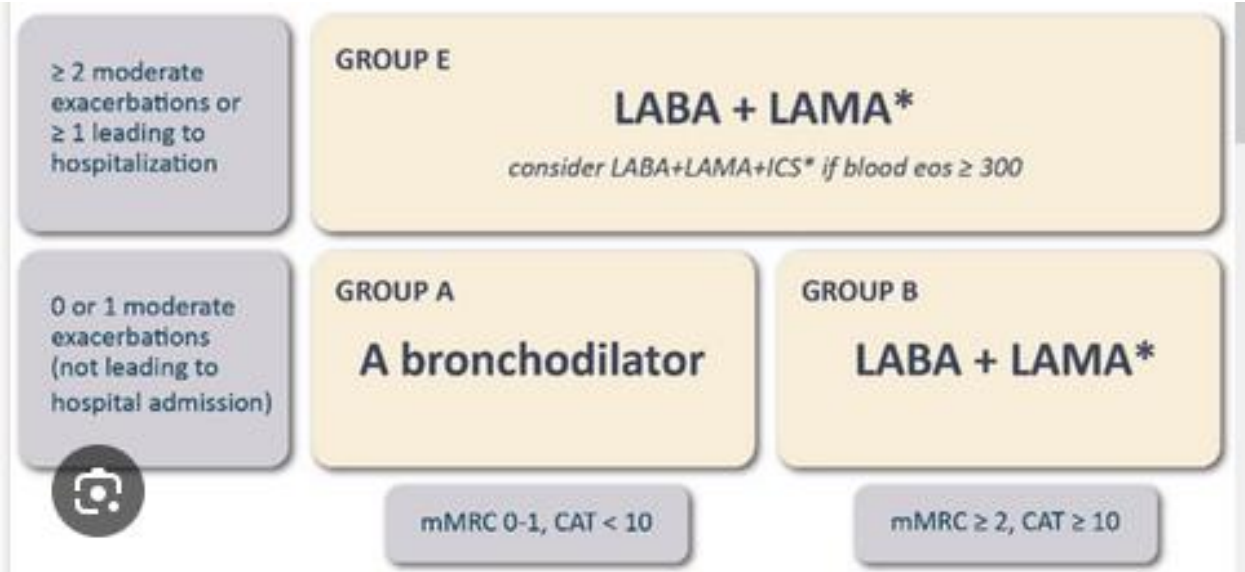
- Adherence to COPD medication regimens is frequently **suboptimal**, and lower adherence is associated with more frequent hospitalization and greater overall cost .
- In an administrative claims **database** study of 14,117 patients with COPD, patients **underused** their prescribed inhalers by at least **50 %**

Technique

- Inhaler technique can be challenging, especially as the techniques for using pMDIs, DPIs, and SMIs are quite different.
- **Inhaler technique should be taught to all patients** .
- The patient's technique **should be reviewed regularly** .

Use of nebulized therapies

- For patients who are **unable to achieve adequate technique** despite a trial of different devices and a valved holding chamber for metered dose inhalers,
- an **alternative option** may be to **switch to maintenance long-acting nebulized** medications



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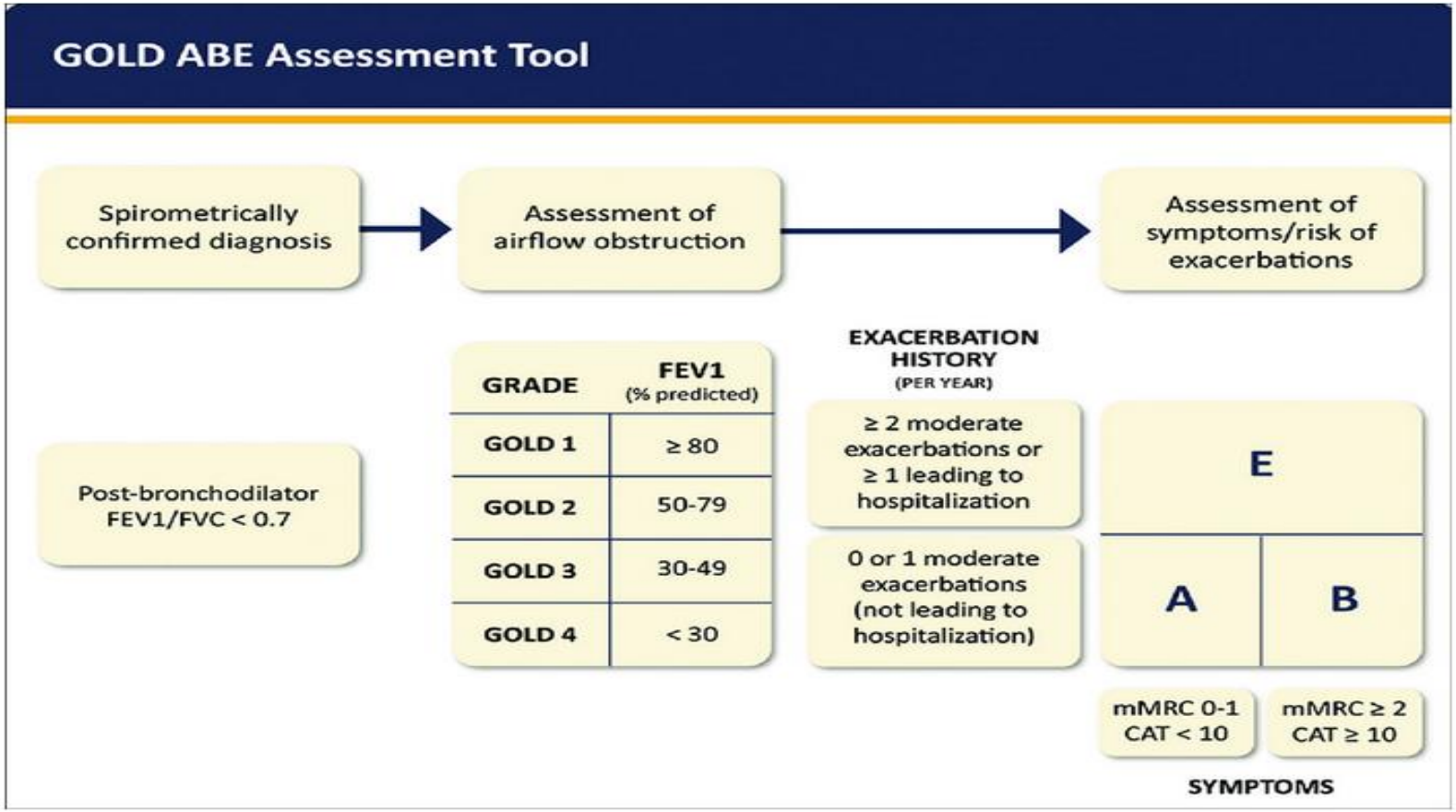

GOLD ABE assessment tool. Exacerbation history refers to exacerbations suffered the previous year. mMRC: modified Medical Research Dyspnea Questionnaire. CAT: COPD Assessment Test. Reproduced with permission from www.goldcopd.org.

Regimen simplicity

- **simplify** inhaler regimens as much as possible, with once or twice daily **single-inhaler triple therapy with LABA, LAMA, and ICS** for most patients with **refractory disease**.

- **minimize** the number of inhalers and number of actuations needed to improve **ease-of-use** and adherence.

Cost and availability

- inhaled medications often remain **expensive**

- costs are a frequent contributor to **poor patient adherence,**

Pulmonary function testing

- patients with refractory symptoms despite optimized inhaled therapies,
- **reevaluate** air flow**, lung volumes**,
  and gas exchange,
- perform ambulatory **pulse oximetry**,
- and measure arterial blood gases at rest.

The **combination** of

- dyspnea and exacerbation **assessment**,
- and physical **examination**
- pulmonary **function testing**,

allows a reasonable assessment of **disease severity** and prognosis

Imaging

patients with **refractory symptoms** of COPD should undergo **CT evaluation** to assess for **comorbid conditions** and new disease processes.

Possible findings include

- new **interstitial lung disease**,
- new **lung cancer**,
- evidence of **pulmonary edema**,
- indirect evidence of **pulmonary hypertension**,
- central airway obstruction, bronchiectasis, or bronchiolitis.

- Patients who continue to smoke or have quit smoking within the past 15 years generally qualify for **CT screening for lung cancer**
- **Low- dose computed tomography.**

Evaluating for comorbid diseases

- including **asthma**, **bronchiectasis**, **lung cancer**, environmental allergies, **coronary heart** disease, heart failure, **pulmonary hypertension**, **obesity**, anemia, gastroesophageal reflux disease, chronic **nasal/sinus disease**, dysphagia or aspiration, immunodeficiency, **sleep-disordered** breathing, **anxiety** and depression, and cognitive impairment

- Evaluating for **these conditions** by thorough history and physical examination often may **reveal** **additional therapeutic options**.

NUTRITIONAL, RESPIRATORY support

- Select patients with severe COPD may also benefit from **supplemental oxygen** improved
- nocturnal **NIV support , nutrition** .
- maximize **physical fitness**,
- receive appropriate **vaccinations** against respiratory infections.

Oxygen

Long-term supplemental oxygen therapy is recommended for persistent chronic hypoxemia

- (**resting arterial oxygen tension [PaO_2] ≤55 mmHg** or
- pulse oxygen saturation **[SpO_2] ≤88 %**

to improve survival.

Less stringent criteria

- (PaO_2 **≤59** mmHg or an SpO_2 **≤89** %) are used if there is evidence of

  cor pulmonale,

  right heart failure, or

  hematocrit >55%.

PHARMACOLOGIC APPROACHES

For patients who have **repeated exacerbations** of COPD despite optimized therapy with a

- long-acting muscarinic agent (LAMA),
- a long-acting beta-agonist (LABA),
- ensifentrine FDE 3-4 I ,
- plus an inhaled glucocorticoid (ICS)

- The **LABAs** formoterol and arformoterol and use a standard nebulizer at a dose of 15 mcg (one vial) twice daily .

- **LAMAs** revefenacin are available by nebulization for maintenance treatment in patients with COPD

- **revefenacin** uses a standard nebulizer with a dose of 175 mcg (one vial) once daily.

- **PDE 3&4 inhibitor** Ensifentrine is used at a dose of 3 mg (one vial) twice daily

Ensifentrine: Drug information

- Pharmacologic Category **Phosphodiesterase-3 Enzyme/Phosphodiesterase-4 Enzyme Inhibitor**
- **prevent the breakdown of c AMP**
- **cAMP PLAYS A VITAL ROLE IN RELAXING AIRWAY SMOOTH MUSCLES AND SUPPRESSING INFLAMMATION**

Ensifentrine

- Nebulization suspension:

  Oral inhalation: 3 mg twice daily.

ICS USE:

formal study of maintenance dosing in COPD is lacking,

- budesonide can be administered by nebulizer 0.25 to 1 mg twice daily (**off-label**), with the higher dose being reserved for patients with concomitant features of COPD and asthma.
- use **0.5 mg twice daily in patients with exacerbations** and the **lower dose for patients without exacerbations** or with adverse effects of ICS such as thrush, voice changes, or recurrent pneumonia.

- potential pharmacologic options include roflumilast oral PDE-4 inhibitor

- Consider for patients **with frequent exacerbations** (≥1 hospital admission per year) despite optimal medical management .
- **Oral: 250 mcg** once daily for **4 weeks**, followed by **500 mcg** once daily.

- The **initial dose** of **250 mcg once daily** is recommended for the first 4 weeks of treatment in an **attempt to improve tolerability**.

- However, this is **not considered a therapeutic dose** and the effect of this approach on long-term tolerability is uncertain.

- in patients **prone to exacerbations**

  Azithromycin, 250 mg daily or 500 mg three times per week, reduces exacerbations

  The optimal duration of therapy is unclear, but **12-month** courses or longer are typical.

Chronic azithromycin therapy may lead to **adverse effects.**

It should be avoided in patients with a **long QT interval**.

Macrolides are associated with **hearing loss** in clinical trials, so **hearing should be assessed periodically.**

dupilumab (IL-4 receptor antagonist)therapy

- (**off-label**) may be helpful in
- **reducing exacerbations and**
- **improving airflow obstruction**

based on **one clinical trial .**

- May consider **as add-on therapy** in patients with **refractory eosinophilic chronic obstructive pulmonary disease** (peripheral blood eosinophils ≥300 cells/mcL) who are inadequately controlled on standard therapies
- **SUBQ:** 300 mg once every other week

For patients with **persistent breathlessness** despite inhaled therapies,

- there are few proven pharmacologic therapies available;
- monitored Low-dose theophylline a trial of theophylline (dosed to trough 5 to 12 mcg/mL)

- may **improve** **lung function** and
- **exercise** **tolerance**;

- however, its use requires **close monitoring** due to the narrow therapeutic window of this agent.

- low-dose **opiates**

- may be helpful in some patients.
- in **one placebo-controlled trial** of 156 patients with moderate to severe COPD and modified Medical Research Council (mMRC) dyspnea scale scores ≥3

use of extended-release morphine (8 to 32 mg daily, increased stepwise) had **no significant effect on breathlessness** intensity or on daily step count but did result in higher discontinuation rates and serious treatment-related adverse events

- **Mucolytics**

Mucoactive agents : Thick, tenacious secretions can be a major problem in patients with COPD, but **there is little evidence that thinning or increasing the clearance rate of secretions induces clinical improvement**.

- **Oral** N-acetylcysteine :

  Thiol derivatives such as **NAC**, **erdosteine**,

  and **carbocysteine** are mucolytic agents designed to sever disulfide bonds of mucoproteins and DNA,

  possibly leading to reduced mucus viscosity.

- NAC also **has antioxidant effects**.

  an oral preparation (NAC, 600 mg twice daily)

  can be initiated on a trial basis and continued if there is symptomatic improvement.

- One **trial (PANTHEON) of 964 patients** with moderate to severe COPD (mean FEV_1 49 % of predicted) found a **reduction in exacerbations** with NAC (**600 mg tablets twice daily**) compared with placebo

- The use of **inhaled NAC** has **no effect** on sputum volume, can induce significant bronchoconstriction, and should not be a part of routine COPD management.

- and **oral glucocorticoids** are sometimes used,
- they have long been used to treat exacerbations in patients with COPD,
- **they are only rarely indicated for chronic use.**

nutrition

- **vitamin D supplementation** was associated with a greater improvement in **inspiratory muscle strength** and **maximal oxygen uptake**

- supplementation with **essential amino acids** (EAA) **may be** of benefit in patients with COPD.

Take home message

Patient with **refrectory COPD** should be reevaluated clinically , inhalers he takes , consider the other medical options ,

manage comorbidities , anxiety , depression to enhance care planning .


Thank You