2023 GOLD Update : Treatment

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Global Initiative for Chronic Obstructive Lung Disease

2023 REPORT

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Goals for Treatment of Stable COPD

Table 4.1

- Relieve Symptoms
- Improve Exercise Tolerance
- Improve Health Status

REDUCE SYMPTOMS

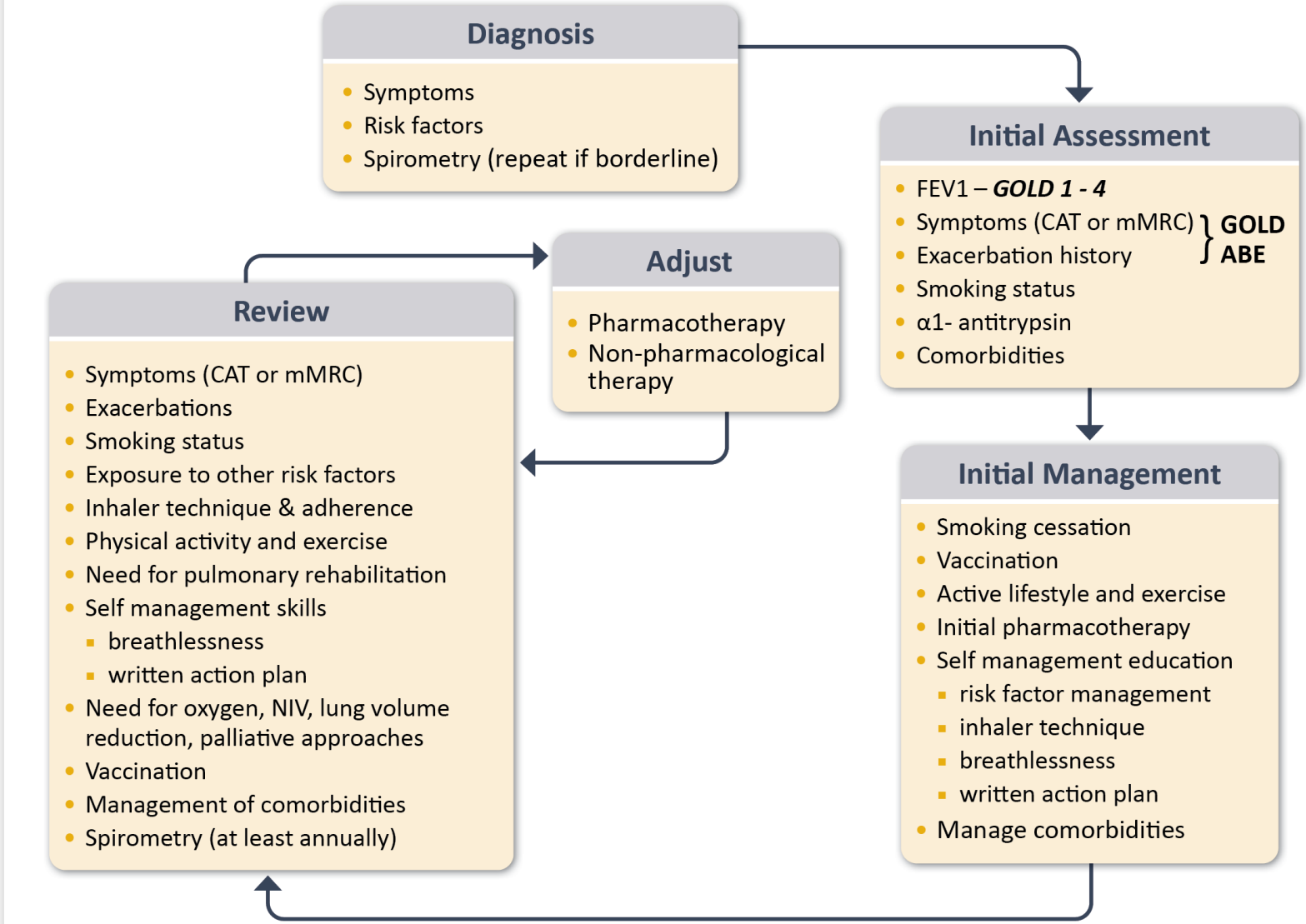
AND

- Prevent Disease Progression
- Prevent and Treat Exacerbations
- Reduce Mortality

REDUCE RISK

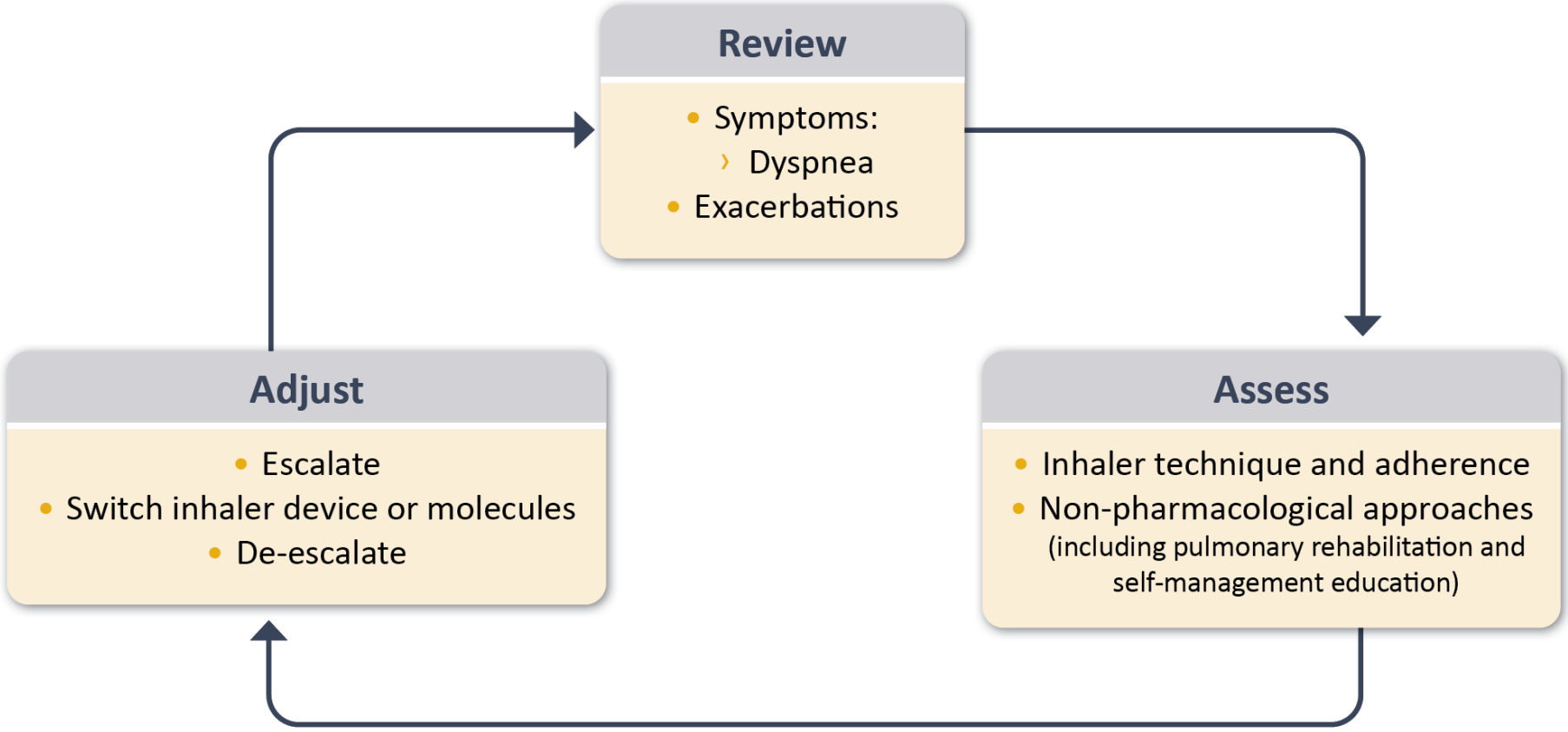
Management of COPD

Figure 4.1

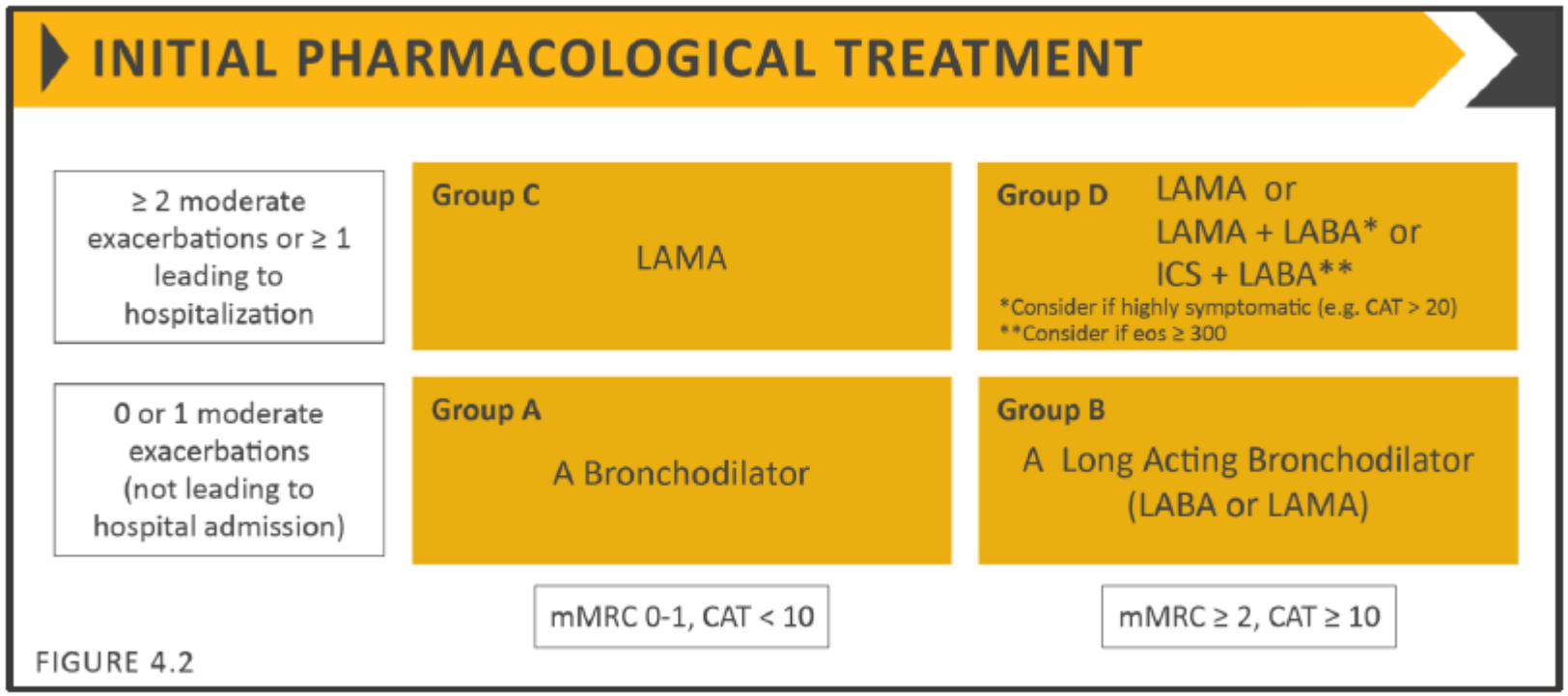


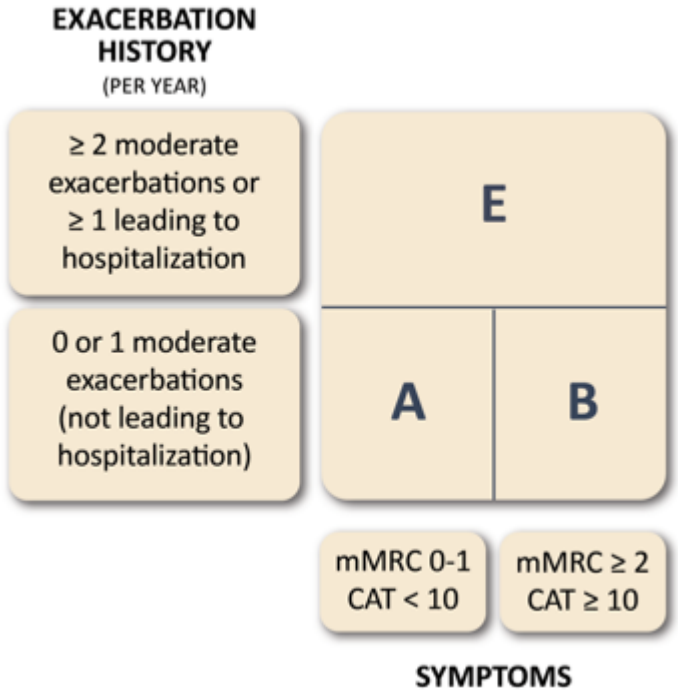
Management Cycle

Figure 4.3



Initial Pharmacological Treatment





Initial Pharmacological Treatment

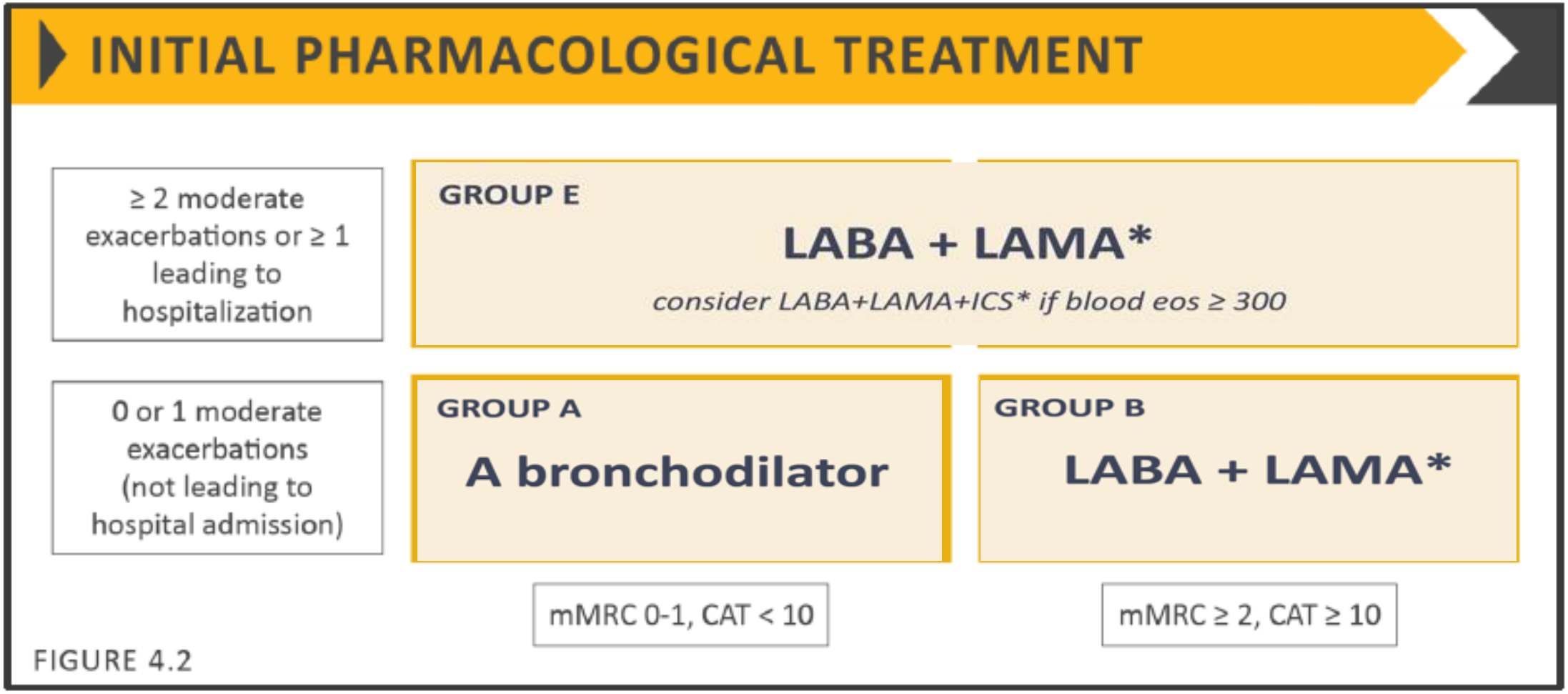
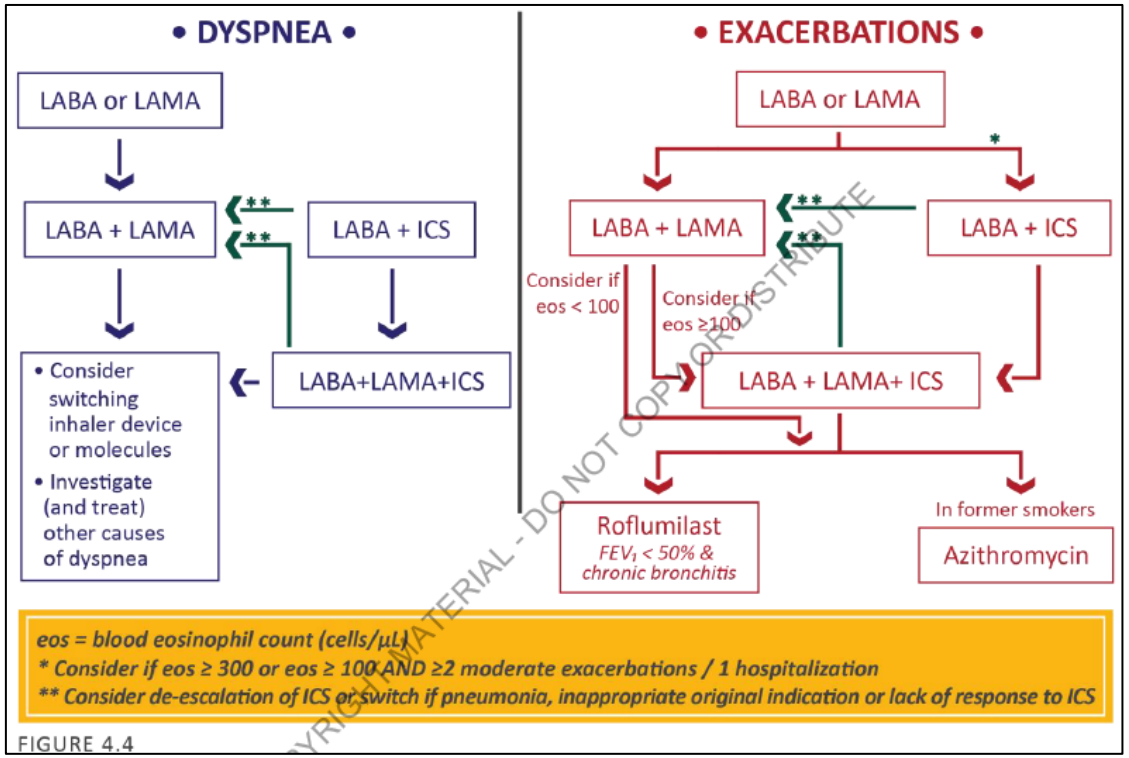
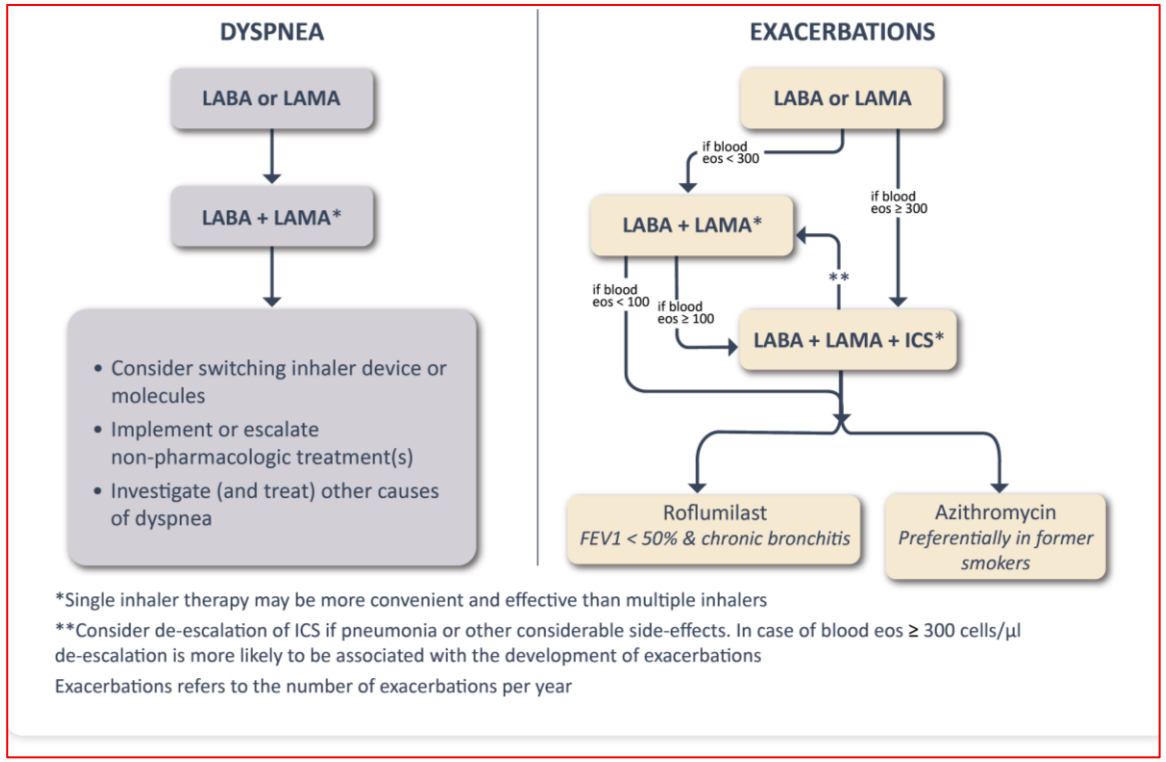


FIGURE 4.2

Follow-up Pharmacological Treatment





Follow-up Pharmacological Treatment

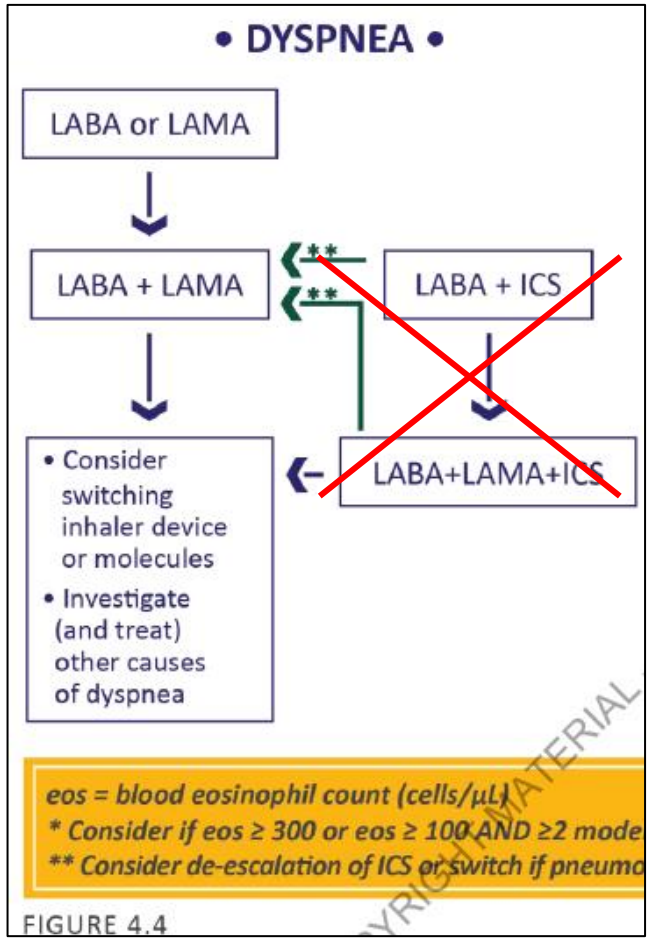
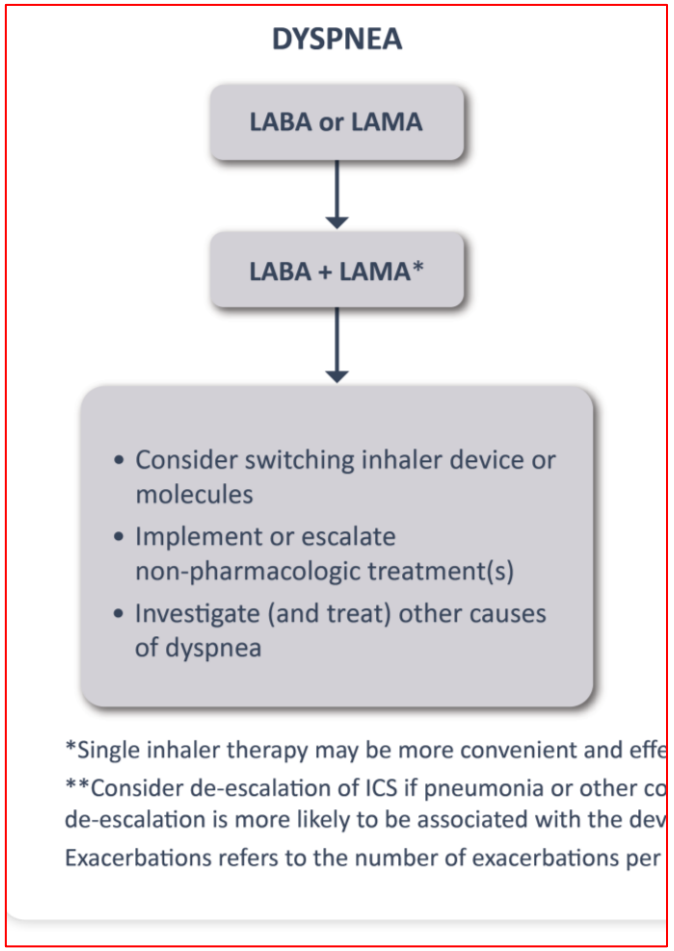
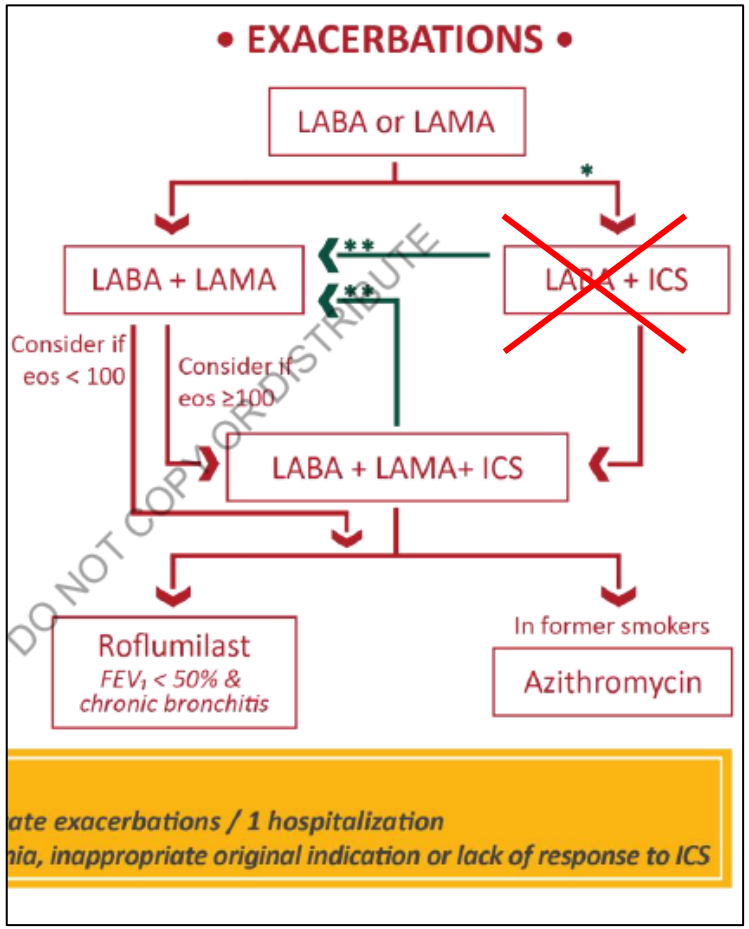
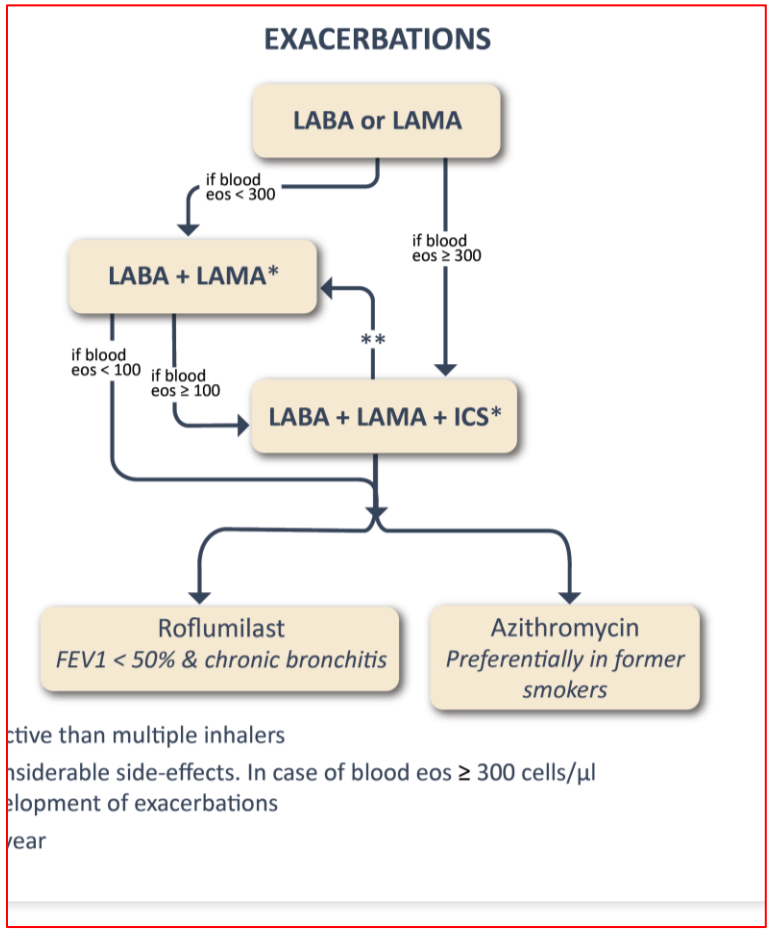


FIGURE 4.4



Follow-up Pharmacological Treatment





Bronchodilators in Stable COPD

Table 3.4

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**
- Regular and as-needed use of SABA or SAMA improves FEV1 and symptoms **(Evidence A)**
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV1 and symptoms **(Evidence A)**
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**
- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**
- Combination treatment with a LABA and a LAMA increases FEV1 and reduces symptoms compared to monotherapy **(Evidence A)**
- Combination treatment with a LABA+LAMA reduces exacerbations compared to monotherapy **(Evidence B)**
- Single inhaler therapy may be more convenient and effective than multiple inhalers

Inhaled Corticosteroids

- Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)**
- Long-term monotherapy with ICS is not recommended **(Evidence A)**
- We do not encourage the use of a LABA+ICS combination in COPD. If there is an indication for an ICS the combination LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore the preferred choice. This combination can be given as single or multiple inhaler therapy.
- If patients with COPD have features of asthma, treatment should always contain an ICS
- Triple inhaled therapy of LABA+LAMA+ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA+ICS, LABA+LAMA or LAMA monotherapy **(Evidence A)**. Recent data suggest a beneficial effect of triple inhaled therapy versus fixed-dose LABA+LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations
- Single inhaler therapy may be more convenient and effective than multiple inhalers

Factors to Consider when Initiating ICS Treatment

Factors to consider when adding ICS to long-acting bronchodilators:

(note the scenario is different when considering ICS withdrawal)

STRONGLY FAVORS USE	**History of hospitalization(s) for exacerbations of COPD[#]**
	≥ 2 moderate exacerbations of COPD per year[#]
	Blood eosinophils ≥ 300 cells/µL
	History of, or concomitant asthma
FAVORS USE	1 moderate exacerbation of COPD per year[#]
	Blood eosinophils 100 to < 300 cells/µL
AGAINST USE	**Repeated pneumonia events**
	Blood eosinophils < 100 cells/µL
	History of mycobacterial infection

[#]despite appropriate long-acting bronchodilator maintenance therapy (see Table 3.4 and Figure 4.3 for recommendations);
*note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

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Anti-inflammatory Therapy in Stable COPD

Oral Glucocorticoids	• Long-term use of oral glucocorticoids has numerous side effects **(Evidence A)** with no evidence of benefits **(Evidence C)**
PDE4 Inhibitors	• In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations: ▪ A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations **(Evidence A)** ▪ A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA+ICS combinations **(Evidence A)**
Antibiotics	• Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A)** • Treatment with azithromycin is associated with an increased incidence of bacterial resistance **(Evidence A)** and hearing test impairments **(Evidence B)**
Mucoregulators and Antioxidant Agents	• Regular treatment with mucolytics such as erdosteine, carbocysteine and NAC reduces the risk of exacerbations in select populations **(Evidence B)**

Adherence to inhaled COPD medications

- Adherence is defined as the process by which a person takes their medication as prescribed by healthcare provider.
- Adherence to therapy is challenging issue in any chronic condition including COPD
- Non-adherence to COPD medication has been associated with
  - ✓poor symptom control,
  - ✓increase risk of exacerbation,
  - ✓increased healthcare utilization and costs,
  - ✓decreased health-related quality of life and
  - ✓higher mortality risk.

Adherence to inhaled COPD medications

- The adherence to inhaled medication is generally low, even in very severe disease.
- Non-adherence rates to COPD medication of 22% to 93%, with over half of the included studies reporting non-adherence in >50% of subjects.
- High-income countries – many used pharmacy claim data
- Self-reports are inaccurate as people generally over-report medication use

Bhattarai B *et al*. Respir Care. 2020 Nov;65(11):1738-1750.

Adherence to inhaled COPD medications

- To improve COPD medication adherence

⇒ A better understanding of the disease and drug therapy, as well as greater trust in healthcare professionals

⇒ Self-management education

⇒ Multi-component intervention with education, motivational or behavioral components

Other Pharmacological Treatments

Table 3.7

Alpha-1 Antitrypsin Augmentation Therapy	• Intravenous augmentation therapy may slow down the progression of emphysema **(Evidence B)**
Antitussives	• There is no conclusive evidence of a beneficial role of antitussives in people with COPD **(Evidence C)**
Vasodilators	• Vasodilators do not improve outcomes and may worsen oxygenation **(Evidence B)**

Pulmonary Rehabilitation, Self-Management and Integrative Care in COPD

Table 3.8

Pulmonary Rehabilitation	• Pulmonary rehabilitation improves dyspnea, health status and exercise tolerance in stable patients **(Evidence A)** • Pulmonary rehabilitation reduces hospitalization among patients who have had a recent exacerbation (≤ 4 weeks from prior hospitalization) **(Evidence B)** • Pulmonary rehabilitation leads to a reduction in symptoms of anxiety and depression **(Evidence A)**
Education and Self-Management	• Education alone has not been shown to be effective **(Evidence C)** • Self-management intervention with communication with a health care professional improves health status and decreases hospitalizations and emergency department visits **(Evidence B)**
Integrated Care Programs	• Integrative care and telehealth have no demonstrated benefit at this time **(Evidence B)**

Evidence Supporting a Reduction in Mortality

Therapy	RCT*	Treatment effect on mortality	Patient characteristics
Pharmacotherapy			
LABA+LAMA+ICS[1]	Yes	Single inhaler triple therapy compared to dual LABD therapy relative risk reduction: IMPACT: HR 0.72 (95% CI: 0.53, 0.99)[1a] ETHOS: HR 0.51 (95% CI: 0.33, 0.80)[1b]	Symptomatic people with a history of frequent and/or severe exacerbations
Non-pharmacological Therapy			
Smoking cessation[2]	Yes	HR for usual care group compared to intervention group (smoking cessation) HR 1.18 (95% CI: 1.02, 1.37)[2]	Asymptomatic or mildly symptomatic
Pulmonary rehabilitation[3#]	Yes	Old trials: RR 0.28 (95% CI 0.10, 0.84)[3a] New trials: RR 0.68 (95% CI 0.28, 1.67)[3b]	Hospitalized for exacerbations of COPD (during or ≤ 4 weeks after discharge)
Long-term oxygen therapy[4]	Yes	NOTT: ≥ 19 hours of continuous oxygen vs ≤ 13 hours: 50% reduction[4a] MRC: ≥ 15 hours vs no oxygen: 50% reduction[4b]	PaO_2 ≤ 55 mmHg or < 60 mmHg with *cor pulmonale* or secondary polycythemia
Noninvasive positive pressure ventilation[5]	Yes	12% in NPPV (high IPAP level) and 33% in control HR 0.24 (95% CI 0.11, 0.49)[5]	Stable COPD with marked hypercapnia
Lung volume reduction surgery[6]	Yes	0.07 deaths/person-year (LVRS) vs 0.15 deaths/person-year (UC) RR for death 0.47 (p = 0.005)[6]	Upper lobe emphysema and low exercise capacity

*RCT with pre-specified analysis of the mortality outcome (primary or secondary outcome); #Inconclusive results likely due to differences in pulmonary rehabilitation across a wide range of participants and settings.

CHAPTER 5: MANAGEMENT OF EXACERBATIONS

GOLD definition of COPD exacerbation

- 2022 : An acute worsening of respiratory symptoms that results in additional therapy

- 2023

An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations

The Rome Proposal

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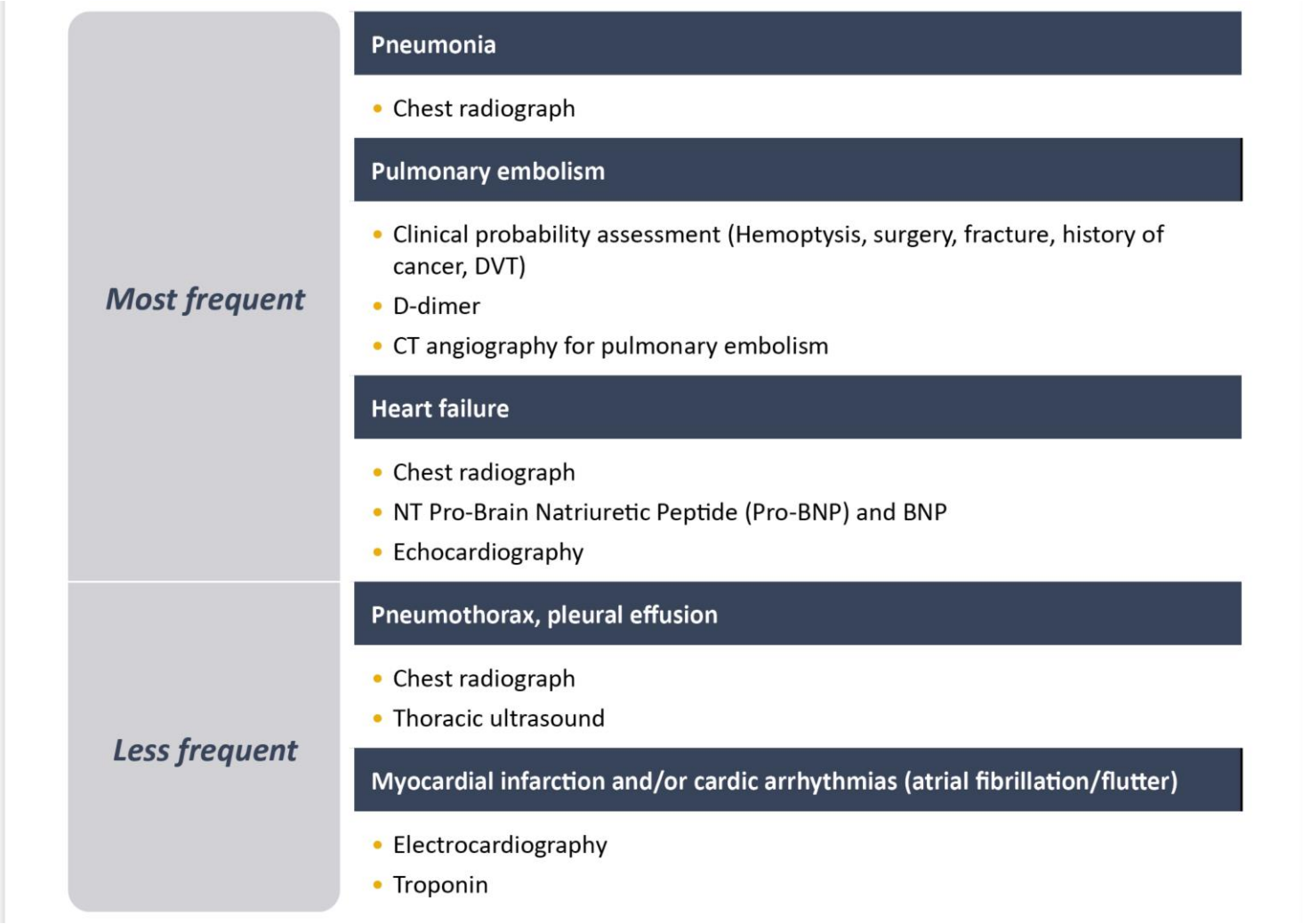
Am J Respir Crit Care Med. 2021 Dec 1;204(11):1251-1258

COPD exacerbation: Consider differential diagnosis



Diagnosis and Assessment

Table 5.2

1.	Complete a thorough clinical assessment for evidence of COPD and potential respiratory and nonrespiratory concomitant diseases, including consideration of alternative causes for the patient's symptoms and signs: primarily pneumonia, heart failure, and pulmonary embolism.
2.	**Assess:** a. Symptoms, severity of dyspnea that can be determined by using a VAS, and documentation of the presence of cough. b. Signs (tachypnea, tachycardia), sputum volume and color, and respiratory distress (accessory muscle use).
3.	Evaluate severity by using appropriate additional investigations such as pulse oximetry, laboratory assessment, CRP, arterial blood gases.
4.	Establish the cause of the event (viral, bacterial, environmental, other).

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; VAS = visual analog scale.

The Grading of severity of exacerbation

- Mild (treated with short acting bronchodilators only, SABDs)
- Moderate (treated with SABDs and oral corticosteroids ± antibiotics)
- Severe (patients required hospitalization or visits the emergency room). Severe exacerbation may also be associated with acute respiratory failure

- The current grading of the severity of an ECOPD, based on post facto use of healthcare resources, is a major limitation of the current definition
- Because of global variability in the available resources to treat patients and local customs affecting the criteria for hospital visits and admission, there is substantial variability in reported ECOPD outcomes.

Classification of the Severity of COPD Exacerbations

Severity	Criteria for judging severity
Mild (default)	• Dyspnea VAS <5 • RR <24 breaths/min • HR <95 bpm • Resting Sa_{O_2} ⩾92% breathing ambient air (or patient's usual oxygen prescription) AND change ⩽3% (when known) • CRP <10 mg/L (if obtained)
Moderate (meets at least three of five*)	• Dyspnea VAS ⩾5 • RR ⩾24 breaths/min • HR ⩾95 bpm • Resting Sa_{O_2} <92% breathing ambient air (or patient's usual oxygen precription), AND/OR change >3% (when known) • CRP ⩾10 mg/L If obtained, ABG may show hypoxemia (Pa_{O_2} ⩽60 mmHg) and/or hypercapnia (Pa_{CO_2} >45 mmHg) but no acidosis (pH >7.35)
Severe	• ABG show hypercapnia and acidosis (Pa_{CO_2} >45 mmHg and pH <7.35)

Am J Respir Crit Care Med. 2021 Dec 1;204(11):1251-1258

Treatment setting

- The goals of treatment for COPD exacerbations are to minimized the negative impact of the current exacerbation and prevent the development of subsequent events.

- Depending on the severity of an exacerbation and/or the severity of the underlying disease, an exacerbation can be managed in either the outpatient or inpatients setting.

- More than 80% of exacerbations are managed on an outpatient basis with pharmacological therapies including bronchodilators, corticosteroids, and antibiotics.

Potential Indications for Hospitalization Assessment

- Severe symptoms such as sudden worsening of resting dyspnea, high respiratory rate, decreased oxygen saturation, confusion, drowsiness
- Acute respiratory failure
- Onset of new physical signs (e.g., cyanosis, peripheral edema)
- Failure of an exacerbation to respond to initial medical management
- Presence of serious comorbidities (e.g., heart failure, newly occurring arrhythmias, etc.)
- Insufficient home support

*Local resources need to be considered

Key Points of the Management of Exacerbation

- Short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation **(Evidence C)**
- Systemic corticosteroids can improve lung function (FEV1), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not normally be more than 5 days **(Evidence A)**
- Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should normally be 5 days **(Evidence B)**
- Methylxanthines are not recommended due to increased side effect profiles **(Evidence B)**
- Non-invasive mechanical ventilation should be the first mode of ventilation used in COPD patients with acute respiratory failure who have no absolute contraindication because it improves gas exchange, reduces work of breathing and the need for intubation, decreases hospitalization duration and improves survival **(Evidence A)**

Glucocorticoids

- Systemic glucocorticoids in COPD exacerbation
  - Improve recovery of time
  - Improve lung function (FEV1), Improve oxygenation
  - Improve risk of early relapse, treatment failure, and length of hospitalization
- 40mg prednisolone per day for 5 days is recommended.
- Longer courses of oral corticosteroid

  ⇒Increased risk of pneumonia and mortality.
- Oral prednisolone is equally effective to IV administration
- Nebulized budesonide alone may be suitable and provide similar benefits to IV methylprednisolone.

Glucocorticoids

- Even short bursts of corticosteroids are associated with

  ⇒ Increased risk of pneumonia, sepsis and death.

- Recent studies suggest that glucocorticoids may be less efficacious to treat acute COPD exacerbation in patient with lower levels of blood eosinophils and more trials of steroid-sparing treatment regimens are required.

Antibiotics

- Antibiotics reduce the risk of
  - ✓short-term mortality by 77%,
  - ✓treatment failure by 53% and
  - ✓sputum purulence by 44%.
- Antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms:
  - ✓increased in dyspnea, sputum volume, and sputum purulence.
  - ✓have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms;
  - ✓or mechanical ventilation.
- Duration of therapy : 5 days.

Recommendations for Follow-up

1 – 4 Weeks Follow-up

- Evaluate ability to cope in his/her usual environment
- Review and understanding treatment regimen
- Reassessment of inhaler techniques
- Reassess need for long-term oxygen
- Document the capacity to do physical activity and consider patient eligibility to be enrolled in pulmonary rehabilitation
- Document symptoms: CAT or mMRC
- Determine status of comorbidities

12 – 16 Weeks Follow-up

- Evaluate ability to cope in his/her usual environment
- Review understanding treatment regimen
- Reassessment of inhaler techniques
- Reassess need for long-term oxygen
- Document the capacity to do physical activity and activities of daily living
- Measure spirometry: FEV1
- Document symptoms: CAT or mMRC
- Determine status of comorbidities

Summary

GROUP E

LABA + LAMA*

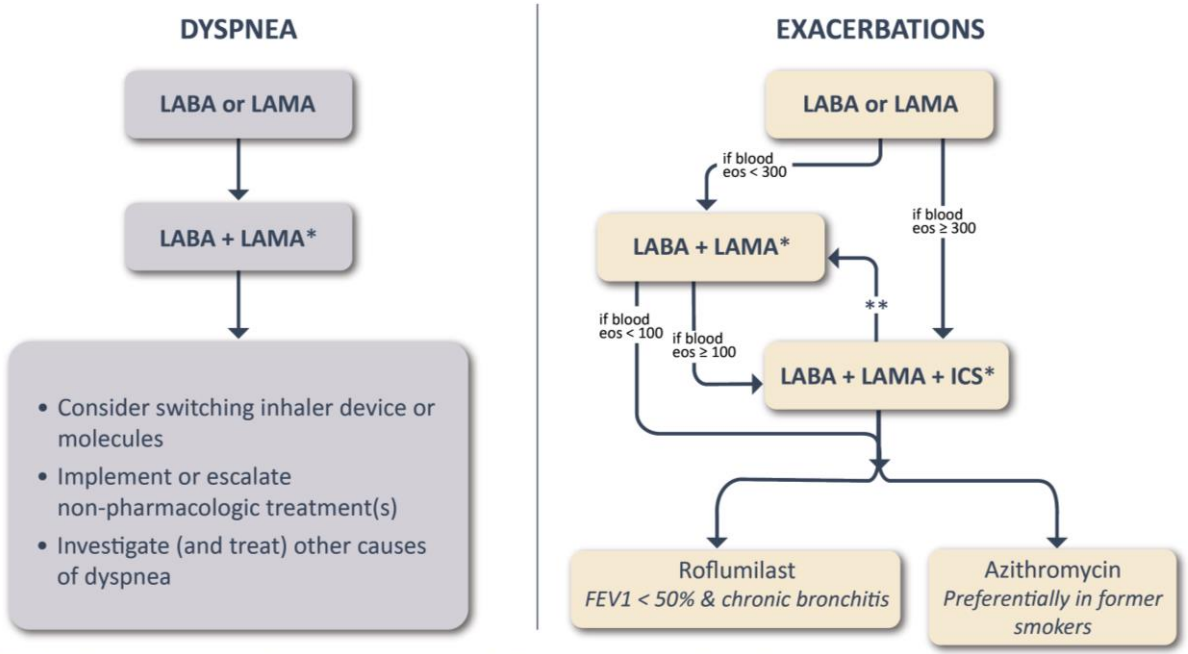
consider LABA+LAMA+ICS if blood eos ≥ 300*

GROUP A

A bronchodilator

GROUP B

LABA + LAMA*



*Single inhaler therapy may be more convenient and effective than multiple inhalers

**Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eos ≥ 300 cells/µl de-escalation is more likely to be associated with the development of exacerbations

Exacerbations refers to the number of exacerbations per year

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