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# Evolution of definitions, classification, and treatment in chronic obstructive pulmonary disease: A comparative review of GOLD reports and international guidelines

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**Abstract:**

This review examines the evolution of chronic obstructive pulmonary disease (COPD) definitions, patient classification frameworks, and pharmacological treatment recommendations across international guidelines, with an emphasis on Global Initiative for Chronic Obstructive Lung Disease (GOLD) and national guidance. Historical and contemporary approaches to symptom assessment, exacerbation risk stratification, and spirometry are contrasted, and evidence is synthesized for bronchodilator-based initial therapy, escalation to dual and triple therapy, and selective inhaled corticosteroid use. Updates on biomarkers and treatable traits are appraised, areas of alignment and divergence among guideline bodies are discussed, and implications for individualized treatment planning and implementation in clinical practice are highlighted. Finally, evidence gaps and research priorities to support risk-based, outcomes-driven COPD care are defined.

**Keywords:**

Bronchodilator agents, chronic obstructive, pulmonary disease, risk assessment, spirometry, symptom assessment

## Introduction

Clinical guidelines are systematically developed statements designed to help practitioners and patients decide on appropriate healthcare for specific clinical situations,[1] enabling physicians to manage individual cases in accordance with these recommendations.[2] Numerous guidelines regarding chronic obstructive pulmonary disease (COPD) have been developed over the years, and many countries have produced their own guidance based on local resources and clinical tra-

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ditions. This article reviews guidelines published in the literature over the past 15 years, from 2011 to the present.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) Committee has pioneered COPD guidance for over two decades. Its first guideline was published in 2001 and has been updated regularly since 2011. The GOLD committee proposed a composite assessment using the ABCD (Assessment of symptoms, Burden of disease, COPD exacerbation risk, and Degree of airflow limitation) approach in 2011, after studies demonstrated that the use of airflow limitation alone could not predict symptom burden and quality of life.[3–5] The diagnosis of COPD is confirmed spirometrically by a ratio of forced expiratory volume in 1 second to forced vital capacity ($FEV_1$/FVC) below 70%; however, patients were classified by predicted $FEV_1$%.

- GOLD grade 1: $FEV_1$ ≥80% predicted,
- GOLD grade 2: $FEV_1$ between 50% and 79% predicted,
- GOLD grade 3: $FEV_1$ between 30% and 49% predicted, and
- GOLD grade 4: $FEV_1$ <30% predicted.

After diagnosis and spirometric grading, patients were categorized into ABCD groups based on symptom assessment using the COPD Assessment Test (CAT) or the Modified Medical Research Council Scoring System (mMRC), and documentation of emergency visits or prior COPD exacerbations (Table 1).

- **Group A:** Asymptomatic patients (CAT <10 or mMRC <2) without exacerbations (GOLD 1–2 and <2 exacerbations/year); a short-acting beta-agonist (SABA) or short-acting anticholinergic (SAMA) bronchodilator (BD) was recommended (Appendix 1).
- **Group B:** Symptomatic patients without exacerbations (GOLD 1–2 and <2 exacerbations/year, with mMRC ≥2 or CAT ≥10); a long-acting beta-agonist (LABA) or long-acting anticholinergic (LAMA) BD was recommended.
- **Groups C and D:** Asymptomatic (Group C) or symptomatic (Group D) patients with frequent exacerbations (GOLD 3–4 and ≥2 exacerbations/year) (Groups C and D) were recommended LAMA therapy alone or a combination of LABA and inhaled corticosteroid (ICS).

LABA+ICS is recommended as first-line treatment for patients suspected of having coexisting COPD and asthma (ACOS). In Group D patients, exacerbations may persist despite dual (LABA+LAMA) and triple (LABA+LAMA+ICS) therapy used as second-and third-line treatments.

**The 2007 German national guideline** provided recommendations for COPD diagnosis and treatment.[6,7] Consistent with the 2001 and 2007 GOLD reports, airflow limitation was graded using the GOLD 1–4 staging. Symptom scoring with CAT or mMRC was not endorsed; a phenotypic assessment was favored instead. Short acting bronchodilators were advised at stage 1, with the addition of a long acting bronchodilator at stage 2. For patients with frequent exacerbations, inhaled corticosteroids were added at stage 3. In stage 4, long term oxygen therapy and/or surgical options were recommended. Combination LABA–LAMA therapy was recommended from stage 2 onward. Use of inhaled corticosteroids was further supported in individuals with $FEV_1$ less than 50% predicted who had been hospitalized for COPD or had exacerbations requiring systemic steroids or antibiotics in the preceding year.

**The 2010 French guideline**[8] graded airflow limitation from 1 to 4 in line with GOLD 2007 and assessed symptoms using mMRC alone. Patients were grouped by symptom pattern: episodic dyspnea, daily exertional dyspnea, and a third category comprising frequent exacerbators despite regular bronchodilator therapy with severe airflow limitation. Treatment recommendations were tiered accordingly: SABA, SAMA, or their combination for episodic dyspnea; LABA, LAMA, or their combination for daily exertional dyspnea. For recurrent exacerbations, ICS+LABA or LABA+LAMA were advised, with escalation to triple therapy (ICS+LABA+LAMA) if control remained inadequate. Theophylline was suggested when inhaled options were insufficient. Roflumilast was not recommended owing to lack of reimbursement; no recommendation was made regarding macrolides; and routine use of N acetylcysteine or carbocysteine was not advised in stable disease.

**The 2013 Portuguese guideline**[9] adopted the GOLD 2011 ABCD framework. In addition to GOLD based spirometric staging, symptoms were assessed using CAT or mMRC, and exacerbation risk was stratified as low (0–1 moderate exacerbations) or high (≥2 moderate or ≥1 severe exacerbation), mirroring GOLD definitions. Phenotypic categorization was recommended, with the frequent exacerbator phenotype defined as two or more exacerbations per year or at least one COPD related hospitalization per

**Table 1: Diagnostic criteria and patient classification across guidelines**

| | Diagnostic criteria | | | | Patient classification | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Airflow limitation | | Symptom classification | | | Exacerbation risk definition | Phenotype used | Patient classification |
| Guideline (year) | $FEV_1$/FVC <0.7 | $FEV_1$/FVC <LLN | | Expected % $FEV_1$ | CAT | mMRC | CCQ | High | +/- | |
| Germany 2007 | + | - | GOLD 2007 | GOLD 1-4 | - | - | - | None | - | GOLD 1-4 |
| France 2010 | + | - | GOLD 2007 | GOLD 1-4 | - | + | - | ≥2 exacerbations/year | + | Dyspnea-based |
| GOLD 2011 | + | - | GOLD 2011 | GOLD 1-4 | + | + | - | ≥2 exacerbations/year OR GOLD 3-4 OR ≥1 hospitalization per year | - | ABCD |
| Portugal 2013 | + | - | GOLD 2011 | GOLD 1-4 | + | + | - | ≥2 moderate exacerbations/year OR ≥1 severe exacerbation/year | + | ABCD |
| Czech Republic 2013 | + | - | GOLD 2011 | GOLD 1-4 | - | - | - | ≥2 exacerbations/year | + | Clinical and ABCD |
| Italy 2014 | - | + | Pre-BD $FEV_1$ | | - | + | - | ≥2 exacerbations/year | - | Pre-BD $FEV_1$ and exacerbations |
| Sweden 2014 | - | + | $FEV_1$ | | + | + | + | ≥2 exacerbations/year | + | Clinical and ABCD |
| Poland 2014 | - | + | GOLD 2011 | GOLD 1-4 | + | + | - | ≥2 exacerbations/year OR $FEV_1$<50% predicted OR ≥1 hospitalization/year | + | Radiological, clinical |
| Finland 2015 | + | - | $FEV_1$ | Low Risk $FEV_1$ ≥50% / High Risk $FEV_1$<50% | Low Risk CAT <10 / High Risk CAT ≥10 | - | - | ≥2 exacerbations/year OR ≥1 hospitalization/year | - | Low- and high-risk |
| Russia 2018 | + | - | GOLD 2011 | GOLD 1-4 | + | + | - | ≥2 exacerbations/year OR ≥1 hospitalization/year | + | Symptom-based |
| NICE 2019 | + | + | GOLD 2011 | GOLD 1-4 | + | + | - | None | - | |
| Spain 2021 | + | - | $FEV_1$ | Low Risk $FEV_1$ ≥50% / High Risk $FEV_1$ <50% | - | + | - | ≥2 exacerbations/year OR ≥1 hospitalization/year | + | Clinical and blood eosinophils |
| Japan 2022 | + | - | GOLD 2011 | GOLD 1-4 | + | None | + | ≥2 exacerbations/year OR ≥1 hospitalization/year | + | Clinical and $FEV_1$ |
| Canada 2023 | + | - | $FEV_1$ | Mild $FEV_1$ ≥80% Moderate-severe $FEV_1$ <80% | Mild CAT <10/ Moderate-severe CAT ≥10 | Mild mMRC=1 Moderate-severe mMRC ≥2 | - | ≥2 exacerbations/year OR ≥1 hospitalization/year | + | Clinical |
| GOLD 2017 | + | - | GOLD 2011 | GOLD 1-4 | + | + | + | ≥2 moderate exacerbations/ year OR ≥1 severe exacerbation/year | - | ABCD |
| GOLD 2019 | + | - | GOLD 2011 | GOLD 1-4 | + | + | + | ≥2 moderate exacerbations/ year OR ≥1 severe exacerbation/year | - | ABCD |
| GOLD 2023 | + | - | GOLD 2011 | GOLD 1-4 | + | + | + | ≥2 moderate exacerbations/ year OR ≥1 severe exacerbation/year | - | ABE |
| GOLD 2025 | Pre-BD and post-BD $FEV_1$/FVC <0.7 + | - | GOLD 2011 | GOLD 1-4 | + | + | - | ≥2 moderate exacerbations/ year OR ≥1 severe exacerbation/year | - | ABE |

$FEV_1$: Forced expiratory volume in 1 second, FVC: Forced vital capacity, LLN: Lower limit of normal, CCQ: Clinical COPD Questionnaire, GOLD: Global Initiative for Chronic Obstructive Lung Disease, CAT: COPD Assessment Test, mMRC: Modified Medical Research Council Scoring System, ABCD: Groups according to GOLD report based on COPD exacerbations and CAT or mMRC, ABE: Airflow limitation, Burden of symptoms, and Exacerbation risk

year. Treatment recommendations were aligned with the GOLD framework, specifying SABA or SAMA for Group A; LABA or LAMA for Group B; LAMA or LABA+ICS for Group C; and LAMA and/or LABA+ICS for Group D. ICS use was recommended in Groups C and D, although no explicit criteria were specified. Theophylline was suggested when better options were unsuitable. Roflumilast was reportedly unavailable at the time, and macrolides, N acetylcysteine, and systemic corticosteroids were not recommended for stable disease.

**A 2013 Czech guideline** adopted and extended the GOLD 2011 ABCD framework.[10] At baseline, COPD was divided into types related to bronchiectasis, chronic bronchitis, and emphysema. Additional subgrouping was advised for patients with a body mass index below 21 kg m−2 and visible muscle atrophy (pulmonary cachectic phenotype); for frequent exacerbators (two or more per year); and for those with features suggestive of type 2 inflammation or asthma overlap, including bronchodilator reversibility, positive bronchial challenge, elevated fractional exhaled nitric oxide (FeNO) and eosinophils, or a prior asthma history (COPD–asthma overlap). SABA or SAMA were recommended for oligosymptomatic patients and for symptomatic relief. Initiation of LABA, LAMA, or their combination was advised for symptomatic patients with post-BD $FEV_1$ 60–80% predicted, and for all patients with post-BD $FEV_1$ <60% predicted. Agent selection was left to clinician or patient preference. Consistent with GOLD 2011, phenotype specific treatment was recommended, particularly for patients in categories B and D under the ABCD approach.

**The Italian Group** suggested that a forced expiratory volume in one second to vital capacity ($FEV_1$/VC) ratio (predicted for age and gender) below the normal range after bronchodilator administration is sufficient to confirm the diagnosis, as age and gender influence normal limits.[11] In symptomatic patients with mMRC grade 1 or higher, bronchodilator therapy was recommended when pre bronchodilator $FEV_1$ was at least 80% predicted, without specification of a particular agent. For those with pre bronchodilator $FEV_1$ below 80% predicted, initiation of LABA or LAMA was advised. Addition of an ICS to LABA was recommended for patients who remained symptomatic despite long acting therapy, had pre bronchodilator $FEV_1$ less than 60% predicted, or experienced two or more exacerbations per year. Use of a single inhaler fixed dose LABA+ICS was suggested to support adherence, and escalation to LAMA+LABA+ICS was noted to improve lung function, quality of life, and hospitalization rates.

**In the Swedish guideline published in 2014**, a post-BD $FEV_1$/FVC ratio lower than the lower limit of normal (LLN) was established as a criterion for COPD diagnosis, rather than a fixed ratio.[12] Airflow limitation was still determined by the predicted $FEV_1$ value, while the use of clinical COPD questionnaires alongside CAT or mMRC in symptomatic assessment was emphasized. The bronchitic type was determined by lung function assessment, and it was also noted that this subtype may predict response to roflumilast. The frequent exacerbator phenotype was defined by a history of two or more exacerbations per year, with a history of more than two exacerbations in two consecutive years considered particularly important. Treatment recommendations were also in accordance with the GOLD ABCD classification. ICS was recommended in Groups C and D for recurrent exacerbations or when predicted $FEV_1$ was less than 50–60%.

**The 2014 Polish guideline** recommends an $FEV_1$/FVC ratio below the LLN for COPD diagnosis.[13] Exacerbation risk was defined as two exacerbations per year or at least one hospitalization, with an $FEV_1$ less than 50% predicted considered an additional risk factor. The guideline classified phenotypes as chronic bronchitic, emphysematous, and frequent exacerbator, whereas ACOS was excluded.

Treatment recommendations were stratified by symptom burden, airflow limitation, and exacerbation risk:

- CAT <10, $FEV_1$ ≥50% , low exacerbation risk: SABA/SAMA.
- CAT ≥10, $FEV_1$ ≥50%, low exacerbation risk: LABA/LAMA.
- CAT <10, $FEV_1$ <50%, high exacerbation risk: LAMA/ICS+LABA.
- CAT ≥10, $FEV_1$ <50%, high exacerbation risk: LAMA±ICS+LABA.

In the **2015 Finnish guideline**,[14] patients were classified according to clinical features, symptom burden, and exacerbation risk. The ACOS phenotype was further defined by specific criteria: a significant BD response (more than 15% predicted $FEV_1$ and at least a 400 mL increase), sputum eosinophilia or elevated FeNO (>50 ppb), and asthma-compatible symptoms before the age of 40 years, in addition to meeting COPD diagnostic criteria. These

subclassifications were combined to form patient groups with low and high exacerbation risk. Low-risk patients were defined as having infrequent prior exacerbations, an $FEV_1$ of at least 50% predicted, and absence of typical ACOS features. For low-risk patients, initial therapy with SABA or SAMA was recommended, with LABA or LAMA advised for more symptomatic individuals. For high-risk patients, LAMA or LABA+ICS was recommended; in those with asthma–COPD overlap (ACOS), LABA+ICS or LABA+LAMA+ICS was preferred.

While the LABA+LAMA combination remains an alternative treatment, the question of which patient group it is most suitable for remains open. Caution is advised regarding the use of ICS in patients with osteoporosis, diabetes mellitus, and pneumonia.

In the **Russian guidelines published in 2014 and 2018**,[15,16] phenotyping was incorporated into the guidelines, including bronchitic, emphysematous, frequent exacerbator, and ACOS phenotypes. LAMA therapy has been shown to reduce subsequent exacerbations,[17,18] and the 2018 Russian guideline pioneered the recommendation of LAMA+LABA as first line therapy for symptomatic patients, representing the earliest national endorsement of this strategy.

Initial therapy:

- Asymptomatic or low symptom burden (mMRC <2 or CAT <10): start with a single long-acting bronchodilator (LAMA or LABA).
- Symptomatic (mMRC ≥2 or CAT ≥10): start with dual bronchodilation (LAMA+LABA).

Asymptomatic patients who experience exacerbations:

- If recurrent, non-infectious exacerbations are identified and features suggest asthma–COPD overlap (ACO) or non-eosinophilic inflammation: switch to ICS+LABA.
- If symptoms persist or exacerbations recur despite ICS+LABA: switch to LABA+LAMA.
- If still uncontrolled: escalate to triple therapy (LAMA+LABA+ICS).

Symptomatic at diagnosis:

- If exacerbations are not controlled on LAMA+LABA: escalate to triple therapy (LAMA+LABA+ICS).

Alternative therapies, selected according to patient phenotype, including theophylline, roflumilast, and macrolides, with or without N-acetylcysteine (NAC), were recommended. **The NICE 2018 guideline**, with a minor update in **2019**,[19] specified key variables—such as $FEV_1$, smoking status, dyspnea severity, exercise capacity, and low Body Mass Index (BMI)—and advised against reliance on multidimensional indices (e.g., BODE [Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity]). Dual bronchodilation was advised for patients with COPD who experience exacerbations or whose dyspnea remains inadequately controlled despite monotherapy. For individuals without concomitant asthma or with a low likelihood of corticosteroid responsiveness, LAMA+LABA was preferred; conversely, LABA+ICS was suggested for those with asthma or an anticipated steroid response. If symptoms remain uncontrolled and patients on LAMA+LABA report daily limitations affecting quality of life, a three-month trial of triple therapy may be considered. After three months, continuation should be determined through a clinician–patient discussion of symptom burden rather than solely on instrument scores (e.g., CAT, MRC). If no improvement is observed, de-escalation to LAMA+LABA should be considered. Among patients on LAMA+LABA who experience either one severe or two moderate exacerbations annually, escalation to triple therapy was recommended. Similarly, for those on LABA+ICS with persistent daily symptoms impairing quality of life or with a history of one severe or two moderate exacerbations per year, triple therapy was advised. The committee also emphasized the need to consider the increased risk of pneumonia when initiating triple therapy and to document the clinical rationale for ongoing ICS use.

The committee noted that there is stronger evidence that triple therapy benefits individuals using LABA+ICS compared to those using LAMA+LABA. For those using LABA+ICS, the evidence indicates that LAMA+LABA+ICS reduces the rate of severe exacerbations, improves $FEV_1$, and does not increase the risk of pneumonia or other serious adverse events.

In **2021, the Spanish guideline** underwent a subsequent update following its 2014 revision.[20,21] After phenotyping into exacerbation-free, ACOS, chronic bronchitic exacerbator, and emphysematous phenotypes, the new guideline was simplified and, similar to the Russian guideline, primarily divided patients into low-and high-

risk categories. The low-risk category comprised individuals with post-bronchodilator $FEV_1$ ≥50% predicted, an mMRC dyspnea score of 0–1, and a history of 0–1 exacerbations without hospitalization in the preceding year. Patients with post-bronchodilator $FEV_1$ <50% predicted, an mMRC score of 2–4, or a history of two or more exacerbations or one hospitalization were classified as high risk. The high-risk group was further stratified into three subgroups: exacerbation-free, non-eosinophilic, and eosinophilic phenotypes.

For low-risk patients, LAMA was recommended as first-line therapy, with escalation to LAMA+LABA if needed. Among high-risk patients without exacerbations, initial treatment with LAMA+LABA was advised. In the non-eosinophilic exacerbation subgroup, LAMA+LABA could be initiated; in the setting of frequent exacerbations or blood eosinophils ≥300 cells/$mm^3$, a switch to LABA+ICS was considered an acceptable alternative. For the eosinophilic exacerbation subgroup, initial dual therapy with LABA+ICS was recommended. Given evidence that triple therapy reduces exacerbations and improves symptoms, escalation to triple therapy was recommended for patients who continued to exacerbate despite dual therapy. Withdrawal of ICS could be considered in patients who were non-eosinophilic and had no exacerbations.

Theophylline was stated to improve dyspnea.

**The Japanese Respiratory Society** issued the sixth update of its COPD guideline in 2022.[22] The guideline emphasized assessing disease severity not only by $FEV_1$ decline but also by exercise intolerance, reduced physical activity, dyspnea intensity, health status (CAT), and exacerbation burden. Pharmacologic therapy is first-line: short-acting bronchodilators are used as needed, and initial maintenance with either a LAMA or a LABA is recommended for patients without asthma. For individuals with asthma–COPD overlap (ACO), initial therapy with LABA+ICS is preferred. If symptoms or exacerbations remain uncontrolled in non-asthmatic patients, escalation from monotherapy to dual bronchodilation (LAMA+LABA), and subsequently to triple therapy, is advised. In ACO, direct escalation to triple therapy is recommended when control is inadequate. The guideline also advises against the rapid addition of ICS and recommends considering ICS withdrawal if benefit is not demonstrated or adverse effects occur. In Japan, ACO is widely accepted, and affected patients have been reported to experience more moderate-to-severe exacerbations and greater $FEV_1$ decline, indicating higher risk.

In **2023, the Canadian Thoracic Society** issued a COPD guideline.[23] Given the clinical heterogeneity of COPD, the document advised against using spirometry alone to determine disease severity. Instead, it prioritized a comprehensive assessment incorporating symptom burden (dyspnea, activity limitation, and impaired health status) and exacerbation risk. Notably, the guideline was based exclusively on randomized controlled trials; expert opinion was not incorporated.

As-needed SABA use was recommended alongside all treatment regimens. Patients were categorized as mild versus moderate-to-severe. Mild COPD was defined by low symptom burden (CAT <10, mMRC 0–1) and $FEV_1$ ≥80% predicted; LAMA or LABA was recommended as first-line maintenance therapy. Moderate-to-severe COPD was defined by CAT ≥10, mMRC ≥2, and $FEV_1$ <80% predicted. Among patients at low exacerbation risk (one or fewer exacerbations in the prior year and no hospitalizations), initial dual therapy with LAMA+LABA was recommended. Patients at high exacerbation risk (more than two moderate exacerbations or more than one severe exacerbation in the prior year) were advised to initiate triple therapy (LAMA+LABA+ICS), preferably via a single-inhaler formulation.

De-escalation—discontinuing ICS from triple therapy or stepping down from dual to monotherapy—is generally not recommended in the absence of significant adverse effects. The guideline did not provide eosinophil-based recommendations, citing its reliance on randomized controlled trial (RCT) evidence and the predominance of eosinophil data from observational studies or post hoc analyses.

As the GOLD committee published the 2017 and 2018 updates,[24] spirometric grades were separated from the ABCD groups. The recommendation for ICS+LABA in Group C was removed, and LABA+LAMA became prominent in Group D. In 2019, it was emphasized that blood eosinophil levels could predict response to ICS, and ICS addition was recommended for patients with levels above 300 cells/μL.[25] Treatment changes were thereafter made according to the patient's symptoms and exacerbation status.

In 2022, new definitions such as early COPD, mild COPD, COPD in young people, and pre-COPD were introduced.

[26] Diffusing capacity for carbon monoxide (DLCO) measurement was highlighted for its prognostic value, particularly in patients whose symptoms were disproportionate to $FEV_1$ severity. Strong recommendations for ICS use were given in cases of prior hospitalization, two or more exacerbations per year, eosinophil counts above 300, or a history of asthma.

In 2023, the term ACO was removed, emphasizing that asthma and COPD are distinct diseases.[27] Patients were reclassified using the ABE (Airflow limitation, Burden of symptoms, and Exacerbation risk) system, and Groups C and D were eliminated. Dual bronchodilator therapy (LABA+LAMA) was recommended for most patients, while triple therapy (LABA+LAMA+ICS) could be considered for those with eosinophil counts >300/μL. In the 2025 update, if no exacerbations occur with LABA+ICS, switching to LABA+LAMA was recommended.[28-30] If dyspnea persists, escalation to triple therapy was advised; if symptoms remain uncontrolled despite triple therapy, ensifentrine, an inhaled phosphodiesterase-3/phosphodiesterase-4 (PDE3/PDE4) inhibitor, may be considered.[31] If eosinophils are <100, LABA+LAMA is preferred; if ≥100, triple therapy is recommended. The benefit-risk balance should be considered when changing treatment, and discontinuation of ICS should be carefully evaluated, especially in patients with high eosinophil counts. Dupilumab is recommended for patients with chronic bronchitis whose eosinophil count is above 300 and whose exacerbations are not controlled with triple therapy.[32,33] In the GOLD 2026 strategy report, a COPD case-detection algorithm was added to address the problem of underdiagnosis of COPD. While the "ABE" system continues, it is recommended that COPD patients who have experienced one or more moderate or severe exacerbations be grouped as Group E, and those who have not reported any exacerbations in the previous year (zero exacerbations) be grouped as Group A or Group B. Mepolizumab has also been added to the treatment recommendations for patients for whom dupilumab is indicated.[28]

In conclusion, the evolution of COPD guidelines reflects a continuous effort toward more personalized and risk-stratified patient care. This evolution is characterized by an increasing focus on disease severity, symptom burden, and exacerbation risk, alongside phenotypic assessment using blood eosinophil levels. There has been a shift toward dual bronchodilation (LAMA+LABA) as the preferred initial therapy, as well as the introduction of novel biological agents.

## Conflicts of Interest

The authors have no conflicts of interest to declare.

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## Author Contributions

Concept – B.A.Y.; Design – B.A.Y., Z.Ç.; Supervision – B.A.Y.; Resource – B.A.Y., Z.Ç.; Analysis and/or Interpretation - B.A.Y., Z.Ç.; Literature Review – B.A.Y., Z.Ç.; Writing – B.A.Y.; Critical Review – B.A.Y.

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## Appendix 1: Treatment options across guidelines

| | Pharmacological treatment | | | Treatment | | |
|---|---|---|---|---|---|---|
| | Inhaler treatment | | | | | Non-Inhaler treatment |
| Guideline (year) | SABA/SAMA | Monotherapy (LABA,LAMA) | Dual therapy (LABA+LAMA/LABA+ICS) | Triple therapy (LABA+LAMA+ICS) | ICS R/D Recommended | |
| Germany (2007) | GOLD 1 | GOLD 2 (LABA) | GOLD 3 (LABA/LAMA+ICS)/ GOLD 4 | GOLD 3/GOLD 4 | None | Mucolytics (restricted), theophylline (third choice) |
| France (2010) | Episodic dyspnea | Daily exercise-induced dyspnea | Daily exercise-induced dyspnea/ frequent exacerbator (LABA+ICS/LABA+LAMA) | Daily exercise-induced dyspnea/ frequent exacerbator | None | Theophylline (third choice) |
| GOLD (2011) | GOLD A | GOLD B/GOLD C (LAMA)/GOLD D (LAMA) | GOLD C (LABA+ICS)/ GOLD D (LABA+ICS) | GOLD D (second choice) | Yes | PDE4 inhibitor, antibiotics, mucolytics, theophylline (during exacerbations) |
| Portugal (2013) | GOLD A | GOLD B/GOLD C (LAMA)/GOLD D (LAMA) | GOLD C (LABA+ICS)/ GOLD D (LABA+ICS) | GOLD D (second choice) | None | Theophylline (third choice) |
| Czech Republic (2013) | Oligosymptomatic | Post-BD $FEV_1$ 60-80% with symptoms/Post-BD $FEV_1$ <60% | Post-BD $FEV_1$ 60-80% and asymptomatic/Post-BD $FEV_1$ <60%/Frequent exacerbators/ACO (LABA+ICS) | Frequent exacerbations/ACO | None | PDE4 inhibitor, antibiotics, mucolytics, theophylline |
| Italy (2014) | Pre-BD $FEV_1$ ≥80% | Pre-BD $FEV_1$ <80% | Pre-BD $FEV_1$ <60% or ≥2 exacerbations/year (LABA+ICS) | ≥2 exacerbations/year | None | PDE4 inhibitor: chronic bronchitis, $FEV_1$ <50% or ≥2 exacerbations |
| Sweden (2014) | GOLD A | GOLD B | GOLD B (LABA+LAMA)/GOLD C (LABA+LAMA)/GOLD D (LABA+LAMA) | GOLD C/GOLD D | None | PDE4 inhibitor |
| Poland (2014) | CAT <10, $FEV_1$ ≥50%, and low risk of exacerbation | CAT ≥10, $FEV_1$ ≥50%, and low risk of exacerbation | CAT <10, $FEV_1$ <50%, and high risk of exacerbations (LABA+ICS) | CAT ≥10, $FEV_1$ <50%, and high risk of exacerbations | None | PDE4 inhibitor, mucolytics, theophylline (selected patients) |
| Finland (2015) | Low-risk group | Low risk but symptomatic/high risk | High risk/ACOS (LABA+ICS) | ACOS | None | Antibiotics, mucolytics |
| Russia (2018) | Symptom relief | Asymptomatic (LAMA/LABA) | Symptomatic (LABA+LAMA)/ Asymptomatic non-infectious (LABA+ ICS) and infectious (LABA+LAMA) recurrent exacerbations | Persistent symptoms or recurrent exacerbations | None | PDE4 inhibitor, antibiotics, mucolytics |
| NICE (2019) | As needed | Relief of breathlessness and exercise limitation | Symptomatic or exacerbator, without asthmatic features (LAMA+LABA) or with asthmatic features (LABA+ICS) | Persistent symptoms or recurrent exacerbations on dual therapy | Yes | PDE4 inhibitor ($FEV_1$ <50% and ≥2 exacerbations despite triple therapy), antibiotics (non-smokers with a productive cough and exacerbations requiring hospitalization), mucolytics (chronic cough), theophylline (uncontrolled symptoms or inhaler misuse) |
| Spain (2021) | As needed | Low risk | High-risk, non-exacerbating, and non-eosinophilic type (LAMA+LABA)/high-risk eosinophilic type (LABA+ICS) | Persistent symptoms or recurrent exacerbations | Yes | PDE4 inhibitor (second-line treatment to prevent exacerbations in patients with chronic bronchitis and severe airflow limitation), antibiotics (frequent exacerbators with ≥3 exacerbations/year), mucolytics (high-dose in exacerbators), theophylline |

**Appendix 1: Cont.**

| | Pharmacological treatment | | | Treatment | | |
|---|---|---|---|---|---|---|
| | Inhaler treatment | | | | | Non-Inhaler treatment |
| Japan (2022) | As needed | Symptomatic non-ACO COPD (LAMA/LABA) | ACO (LABA+ICS)/Persistent symptoms or recurrent exacerbations in non-ACO COPD (LAMA+LABA) | Persistent symptoms or recurrent exacerbations in ACO/non-ACO COPD with recurrent exacerbations and eosinophilia | Yes | Uncontrolled symptoms or exacerbations: mucolytics, theophylline |
| Canada (2023) | As needed | Low symptom burden (CAT <10, mMRC :1, $FEV_1$ ≥80%) | High symptom burden with low exacerbation risk (LAMA+LABA) | High symptom burden with high risk of exacerbations/high symptom burden with low risk of exacerbations and persistent symptoms | No | High symptom burden with high risk of exacerbations and recurrent exacerbations: PDE4 inhibitor, antibiotics, mucolytics |
| GOLD (2017) | GOLD A | GOLD A/GOLD B/GOLD C (LAMA)/GOLD D (LAMA) | GOLD D (LABA+LAMA)/recurrent exacerbations or symptomatic GOLD C (LABA+ICS)/ACOS (LABA+ICS) | Recurrent exacerbations or symptomatic GOLD D | No | PDE4 inhibitor (uncontrolled exacerbations in GOLD D, $FEV_1$<50%, chronic bronchitis, and hospitalization), antibiotics (ex-smokers with uncontrolled exacerbations), mucolytics; theophylline (not recommended when long-acting BDs are available or treatment requirements are met) |
| GOLD (2019) | GOLD A | Group A/Group B/Group C (LAMA)/Group D (LAMA) | Group D (eos ≥300 LABA+LAMA)/recurrent exacerbations or symptomatic Group C (LABA+ICS)/history of asthma (LABA+ICS) | Recurrent exacerbations or symptomatic GOLD D | No | PDE4 inhibitor (uncontrolled exacerbations in GOLD D, $FEV_1$<50%, chronic bronchitis, and hospitalization), antibiotics (ex-smokers with uncontrolled exacerbations), mucolytics; theophylline (not recommended when long-acting BDs are available or treatment requirements are met) |
| GOLD (2023) | GOLD A | GOLD A (LAMA/LABA) | Group B and Group E (LABA+LAMA)/recurrent exacerbations or symptomatic patients with eos <300 (LABA+LAMA) | Recurrent exacerbations or symptomatic patients with eos ≥300 | No | PDE4 inhibitor (uncontrolled exacerbations in GOLD E, $FEV_1$<50%, chronic bronchitis, and hospitalization), antibiotics (ex-smokers with uncontrolled exacerbations), mucolytics; theophylline (not recommended when long-acting BDs are available or treatment requirements are met) |
| GOLD (2025) | GOLD A | GOLD A (LAMA/LABA) | Group B and Group E (LABA+LAMA)/recurrent exacerbations or Symptomatic patients with eos <300 (LABA+LAMA) | Recurrent exacerbations or symptomatic patients with eos ≥300 | Should be evaluated cautiously | PDE4 inhibitor (uncontrolled exacerbations in GOLD E, $FEV_1$<50%, chronic bronchitis, and hospitalization), ensifentrine (uncontrolled dyspnea), antibiotics (ex-smokers with uncontrolled exacerbations), mucolytics; theophylline (not recommended when long-acting BDs are available or treatment requirements are met) |

GOLD: Global Initiative for Chronic Obstructive Lung Disease, LABA: Long-acting beta-agonist, LAMA: Long-acting anticholinergic, ICS: Inhaled corticosteroid, ACOS: Asthma-COPD overlap syndrome, SABA: Short-acting beta-agonist, SAMA: Short-acting anticholinergic