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Updates in the Management of Chronic Obstructive Pulmonary Disease

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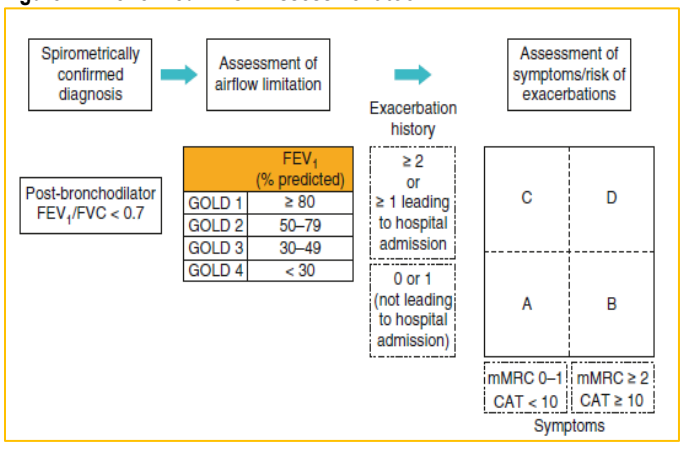
Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by loss of lung function over time. The World Health Organization estimates that by 2030, COPD will be the third leading cause of death worldwide.[1] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report was significantly revised in January 2017.[2] The definition of COPD was broadened to include the impact of chronic respiratory symptoms in addition to persistent airflow limitation. Additional new recommendations include a revised severity assessment of COPD and a shift towards a more personalized treatment approach which includes strategies for both escalating and de-escalating drug therapy when appropriate. This review will highlight pertinent GOLD guideline revisions, and evaluate the evidence supporting the addition of new treatment options.

COPD Severity Assessment

The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on health status, and the risk of future events in order to guide pharmacotherapy.[3] One of the major updates in the GOLD 2017 guidelines is the removal of spirometry from the disease severity assessment. Spirometry remains necessary to make the diagnosis of COPD and is diagnostic for COPD when the post-bronchodilator forced expiratory volume in one second to forced vital capacity (FEV_1/FVC) ratio is less than 0.7.[3] Early iterations of the GOLD guidelines categorized COPD severity by post-bronchodilator FEV_1 alone. However, there is no strong correlation between FEV_1, symptoms and health status.[2] In 2011 the guidelines included a new severity assessment (ABCD groups) of COPD based upon a combination of clinical symptoms, in particular dyspnea, and staging of spirometry. Groups B and D include patients with a high symptom burden and patients in groups C and D are high risk for exacerbations. This ABCD assessment tool was not based on clear evidence supporting its use and did not perform better for predicting health outcomes or mortality.[4-6] Additionally, group D outcomes were modified by two parameters, lung function and/or exacerbation history, which caused confusion for practitioners.[2]

In the 2017 GOLD report, spirometry is not included in the ABCD groups (Figure 1). Spirometry is still recommended to determine the severity of airflow limitation and prognosis, but it does not impact the ABCD categorization. The ABCD groups and the associated pharmacotherapy treatment recommendations are based solely on patient symptoms and history of exacerbations (Figure 1). This revised assessment is meant to provide more precise treatment recommendations based on the parameters influencing the patient's symptoms at any given time.

Figure 1: The refined ABCD Assessment tool

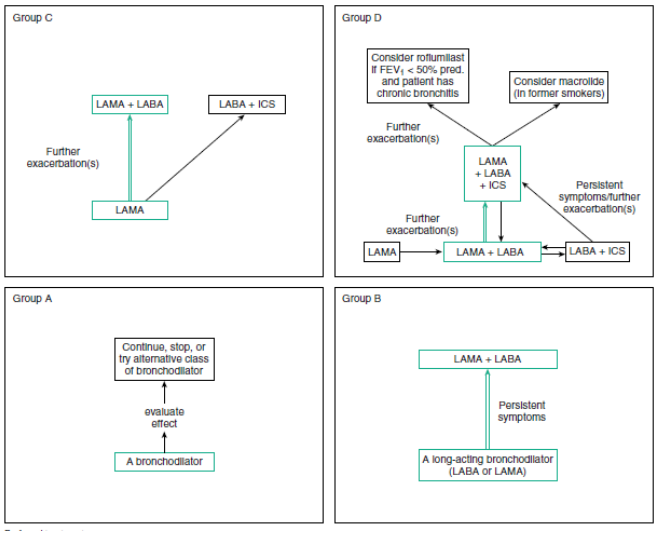


After diagnosis, patients should undergo assessment of dyspnea using the modified British Medical Research Council (mMRC) or symptoms using the COPD Assessment Test (CAT) and their history of exacerbations should be recorded.[3] At each subsequent visit, information on symptoms be collected to help inform necessary changes in pharmacotherapy.

Personalized Treatment Approach

Another advancement in the guidelines is a shift towards a more personalized treatment approach with pharmacological agents. Treatment recommendations are based on the level of symptoms and the individual's risk of exacerbations (ABCD assessment). Previous versions only gave recommendations for initial therapy, while these guidelines include strategies for escalation based on persistent symptoms or de-escalation after resolution of symptoms (Figure 2).

Figure 2: Pharmacologic treatment algorithms by GOLD Grade (highlighted boxes and arrows indicate preferred treatment pathways)



All Group A patients should have a bronchodilator (long acting or short-acting). The previous guidelines recommended only short-acting first line. For Group B patients (high symptom burden but low risk of exacerbation), a long acting bronchodilator is recommended with no preference given to long acting beta agonist (LABA) or long-acting muscarinic antagonist (LAMA). For patients with persistent symptoms on one long acting bronchodilator, combination therapy with LABA+LAMA is recommended. There is no direct evidence supporting recommendations for patients in groups C and D.

De-escalation back to one agent is recommended if combination therapy does not improve symptoms. Another change is the recommendation of a LAMA first line for group C patients (high exacerbation risk). This change is based on data from two clinical trials concluding that LAMA is superior to LABA in prevention of exacerbations.[7,8] In patients with a history of at least one exacerbation in the previous 12 months, tiotropium was found to reduce the annualized exacerbation rate compared to indacaterol (0.61 vs. 0.79)[7] and reduce the number of patients who experienced one or more exacerbation compared to salmeterol (34.4% vs. 38.5%; ARR 4.1%; NNT 25).[8] A LABA/LAMA combination is recommended for those with persistent exacerbations over adding inhaled corticosteroid (ICS) due to the risk of developing pneumonia. Finally, in Group D patients (high exacerbation risk/high symptom burden), LABA/LAMA combination is recommended since it was found to be superior to LABA/ICS in preventing exacerbations (RR

0.89; 95% CI 0.83 to 0.96).[9] The FLAME trial was a 52 week randomized, noninferiority trial comparing indacaterol-glycopyrronium (LABA/LAMA) to salmeterol-fluticasone (LABA/ICS) in patients with a history of at least one exacerbation during the previous year. Overall, 77% of patients in the LABA/LAMA arm had at least one exacerbation, compared with 82% of patients in the ICS/LABA (ARR 5%).[9]

Place in therapy of ICS:

In previous GOLD guidelines, therapy with ICS/LABA was recommended as a first line option in both Group C and D patients based on data that ICS treatment decreases the rate of COPD exacerbations.[10] It appears ICS has a more limited place in therapy with the update. The WISDOM (Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management) study concluded that discontinuing ICS did not increase the exacerbation rate of patients with both severe disease and an exacerbation history who continued on therapy with LABA/LAMA.[11] Also, the FLAME trial found that patients treated with LABA/LAMA experienced fewer exacerbations than those on LABA/ICS.[9] The guidelines suggest that some patients may still benefit from LABA/ICS as a first choice. This includes those with disease suggestive of asthma-COPD overlap as well as patients with a high blood eosinophil count. Blood eosinophil counts appear to identify acute exacerbations and can predict the effects of ICS on exacerbation prevention.[12] However, currently only post hoc analyses of two clinical trials demonstrate those with a higher blood eosinophil count may respond better to therapy with ICS/LABA.[13] Further prospective randomized controlled trials (RCTs) are needed to determine how best to use eosinophil values in clinical practice.

Prophylactic Antibiotics

The current guidelines include a more ambiguous statement regarding the use of prophylactic, continuous antibiotics. In the previous GOLD update, continuous prophylactic antibiotics were not recommended due to insufficient evidence of benefit (Evidence B).[10] The 2017 version does not definitely recommend against the use and states *"more recent studies have shown that regular use of some antibiotics may reduce exacerbation rate"*.[3] A 2015 meta-analysis identified nine randomized controlled trials evaluating the use of macrolides for prevention of COPD exacerbation.[14] Overall, pooled data demonstrated a reduction in the frequency of exacerbations (RR 0.70; 95% CI 0.56-0.87; p<0.01), but no effect on hospitalizations and all-cause mortality. There was also a trend toward increased adverse events and insufficient data beyond 12 months of therapy.[14] The largest study resulted in a decrease in exacerbations by 0.35 exacerbations per patient-year from 1.83 to 1.48 exacerbation per patient-year. [15] Those with hearing impairment, tachycardia or risk for QT prolongation were often excluded from studies.

The 2017 GOLD report recommends considering adding a macrolide (azithromycin) in former smokers who are still experiencing exacerbations despite being on a LABA/LAMA/ICS (Evidence level B). Uptake of prophylactic antibiotics has been slow in practice, largely due to the unknowns of long term widespread use of antibiotics and the potential effects on macrolide resistance, as well as potential cardiovascular complications. Further research is needed to more precisely determine which patients are most likely to benefit from prophylactic therapy.

Roflumilast

Roflumilast is a phosphodiesterase-4 (PDE4) inhibitor used to reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP. Roflumilast has been studied in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations. [3] GOLD recommends it as an option in patients treated with LABA/LAMA/ICS with an FEV1<50% and chronic bronchitis who are still being hospitalized for exacerbations.[3] However, roflumilast only modestly reduced exacerbations in clinical trials and intolerable side effects resulting in discontinuation are common and include diarrhea, nausea and weight loss.[16] Due to the strict study criteria showing a benefit and side effect profile, its place in therapy is limited.

Limitations

There are some methodological flaws in the GOLD report to consider when assessing the clinical recommendations. The intent of the GOLD report is a 'strategy document' for health care professionals. Although recommendations include the quality of underlying evidence based on the source (RCT, observational studies, etc.), the strength of each recommendation is not provided. Likewise, very few recommendations are made based on high quality evidence, including RCTs. The GOLD is also funded by the pharmaceutical industry. Lastly, treatment algorithms remain vague and hard to translate into actionable items as it is hard to define 'persistent symptoms' and 'further exacerbation' without any guidance.

Conclusion

Optimal treatment of COPD relies on management of exacerbations and symptoms. Guidance outlined by GOLD should be reinforced with high quality evidence to determine treatment decisions in patients with COPD.

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