GOLD 2018 Report: A Review

**Jonathan Mitchell, PharmD Candidate 2019[1]**
[1]University of Findlay College of Pharmacy

Abstract

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report provides research-based recommendations on the diagnosis, treatment, and evaluation of COPD. The GOLD 2018 Report was conducted to detail new research gathered between January 2016 and July 2017. This report was produced using a PubMed search for titles approved by the GOLD Science Committee. This article describes new data added to the GOLD Report and provides a review on the diagnosis, treatment and evaluation of COPD patients.
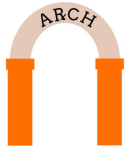
Background

The *Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report* offers research-based recommendations on the treatment and evaluation of chronic obstructive pulmonary disease (COPD). GOLD includes information gathered from January 2016 - July 2017 and contains a revised look at data collected in the 2017 report. This article details changes made to the 2018 Report and provides a review of diagnosis, assessment, treatment, and pharmacotherapy.

Summary of Changes

Allinson et al, investigated the role of adverse early life exposure on FEV_1 and FVC in adults. Early life exposures recorded in this study were infant lower respiratory infection, manual social class, home overcrowding, and pollution exposure. The results of this study suggest that smoking accelerated adult FEV_1 decline and could be associated with early-life exposures influence on FEV_1 and FVC in middle-aged adults.[1] This trial is unique in that it shows how smoking influences adverse early life exposures and how these early life exposures impact adult lung function. These findings allow healthcare practitioners to better identify individuals who might be more susceptible to developing COPD. This data from 2017 was added to corroborate several studies suggesting that processes occurring during development and childhood affect lung growth.[2]

Similarly, a study conducted in China was designed to evaluate the association between ambient particulate matter and adult lung function. This was a cross sectional analysis that examined participants via questionnaire and spirometry.[3] The results showed an association between the amount of ambient particulate matter over 1 year of sampling and the prevalence of COPD. This added to data from the 2017 report warning of the dangers that cigarette smoke, occupational exposures, and urban pollution pose. This study allows healthcare professionals and researchers to identify areas where COPD might be more prevalent and warn the public about the dangers of particulates in the air.

Data collected from two studies recommend confirming a patient's post-bronchodilator FEV1/FVC ratio by repeat spirometry on another occasion if the value is between 0.6 and 0.8.[4] Aaron et al, analyzed two prospective cohorts for frequency of diagnostic instability and diagnostic reversals, and determined that using only one spirometry measurement was not reliable in diagnosing COPD in patients with mild to moderate airflow limitations.[4] Another study by Schermer et al, looked at shifts in obstructed versus non-obstructed diagnostic criteria and found that patients often changed from non-obstructed COPD to obstructed COPD based on BMI, older age, and smoking status among other factors. These results suggest that the use of a single spirometry value in diagnosing a patient with COPD may be inappropriate, and that multiple spirometry tests could allow for more efficient treatment. If a patient's FEV1/FVC is less than 0.6, it is unlikely that this value will improve at that visit.[4] The GOLD Report recommends classifying airflow limitation in patients with COPD as FEV1/FVC <0.7. This update from Aaron et al, allows healthcare practitioners to more accurately assess patients with COPD.[4-6]

Several studies have been conducted on the qualities of the GOLD spirometric grading system, and a new study suggests that exacerbation rates vary greatly during follow up. A longitudinal prospective study by Han et al, focused on individuals between 40 and 80 years old with COPD and their yearly exacerbation frequency. 1105 participants met the criteria and 49% had at least one exacerbation during the three year follow-up. In patients with exacerbations during the three year follow up period, few had two or more exacerbations per year. Patients with consistent exacerbation patterns were associated with higher baseline symptom burden, CT airway abnormalities, and high interleukin-15 and 8 concentrations.[7] This data is relevant to healthcare practitioners because it would allow them to more readily identify COPD patients who would have consistent exacerbations. Recognizing consistent exacerbation patterns would aid practitioners' efforts in treating COPD.[7]

Another study added to the GOLD 2018 Report was conducted on the effects of e-cigarette use on participant's airways. [8] Sputum samples from tobacco smokers, e-cigarette users, and nonsmokers were analyzed and it was determined that e-cigarette users had increased markers for inflammation than nonsmokers. The results of this study suggest that e-cigarette use alters the body's innate immune system and causes changes similar to those seen in those who smoke tobacco.[8] This study is beneficial to healthcare practitioners working with patients who may be interested in switching from regular cigarettes to e-cigarettes and provides evidence that e-cigarettes may not be a healthier alternative to cigarettes.[8]

Data on the efficacy of triple therapy with LABA/LAMA/ICS is limited, so researchers designed the FULFIL (Lung Function and Quality of Life Assessment in Chronic Obstructive Pulmonary Disease with Closed Triple Therapy) to compare participants with COPD receiving once-daily triple therapy and twice-daily ICS/LABA therapy.[9] The FULFIL trial was a randomized, double-blind, double-dummy, study occurring over 24 weeks with co-primary endpoints of change from baseline in trough FEV_1 and change in St. George's Respiratory Questionnaire score. This is a standardized assessment completed by patients to measure the impact of airway disease on health and perceived quality of life.[10] The results of this study suggest that the use of single-inhaler triple therapy is beneficial when compared to ICS/LABA therapy in patients with severe COPD. This information is crucial for healthcare practitioners treating patients with advanced COPD.[9]

Another trial conducted on the efficacy of triple therapy in patients with COPD was the TRINITY trial.[11] This was a double-blind, parallel-group, randomized control trial comparing treatment with extrafine beclometasone dipropionate (BDP), formoterol fumarate (FF), and glycopyrronium bromide (GB) (fixed triple) versus tiotropium and BDP/FF with tiotropium (open triple). Included participants were required to have an FEV_1 <50%, at least one moderate to severe COPD exacerbation in the previous 12 months, and a COPD Assessment Test (CAT) score of at least ten. A CAT score is generated based on an eight-item questionnaire designed to evaluate the impact of a patient's COPD

symptoms. 1078 patients received fixed triple, 1075 received tiotropium, and 538 received open triple. The fixed triple arm reported moderate-to-severe exacerbation rates of 0.46 (95% CI 0.41-0.52). These results were 0.57 (95% CI 0.52-0.63) for the tiotropium arm and 0.45 (95% CI 0.39-0.52) for the open triple arm. Fixed triple proved to be superior to tiotropium (0.80 [95% CI 0.69-0.92], p=0.0025) when comparing rates of moderate-to-severe exacerbation rates. Adverse events were reported by 55% of patients in the fixed triple, 58% of patients receiving open triple, and 58% of patients receiving tiotropium. The results of this trial concluded that treatment with fixed triple therapy was beneficial over tiotropium in patients with symptomatic COPD, $FEV_1 < 50\%$, and a history of exacerbations.[11]

A randomized controlled trial performed on azithromycin and its benefit in COPD was added to the GOLD 2018 Report.[12] This study evaluated azithromycin and its ability to decrease exacerbations in participants with COPD at an increased risk for exacerbations. Patients excluded from this trial were those without hearing loss, resting tachycardia, or prolonged QT interval. Of 1142 patients, 570 were randomly assigned to receive 250mg azithromycin daily, and 572 were randomly assigned to receive placebo.[14] Participants completed these treatments for 1 year in addition to their normal therapies. Median time to exacerbation was 266 days (95% CI 227-313) in the azithromycin arm and 174 days (95% CI 143-215) in the placebo arm (P<0.001).[12] Participants were evaluated using St. George's Respiratory Questionnaire, and patients treated with azithromycin saw more improvement in these

scores than those treated with placebo (SD decrease of 2.8±12.1 compared to 0.6±11.4, P=0.006).[12] The results of this trial concluded that patients taking azithromycin 250 milligrams daily for a year along with traditional therapy had a decrease in the frequency of exacerbations and improved quality of life over those taking placebo. This evidence supports recommending macrolide antibiotics for patients with an increased risk of exacerbations to reduce exacerbations and improve quality of life.[12]

Another study which added data to the GOLD review was a randomized clinical trial designed to evaluate the effect of adding home noninvasive ventilation (NIV) to home oxygen therapy.[13] Researchers were interested in knowing whether or not this addition would prolong time to readmission or death in patients with COPD and persistent hypercapnia following an exacerbation. 59 patients were randomized to home oxygen alone, while 57 patients received home oxygen plus home NIV. Outcomes included the time to readmission or death within 12 months (adjusted for previous COPD admissions), previous use of long-term oxygen, age, and BMI. The results suggest that within this patient population the addition of NIV to home oxygen prolonged the time to either readmission or death within 12 months. This data is important to individuals using home oxygen therapy and shows how health outcomes might be improved in patients with COPD following an admission.[13]

A study conducted on the association between ambient particulate matter and COPD in China assessed questionnaires and spirometry values of ≥20 year old residents of four different cities. An increase in

particulate matter with a median aerodynamic diameter less than 2.5μm ($PM_{2.5}$) of 10 μg/m^3 was associated with a 26 ml decrease in FEV_1 (95% CI -43 to -9), a 28 ml decrease in FVC (-49 to -8), and 0.09% decrease in FEV_1/FVC (-0.170 to -0.010).[14] These results suggest that exposure to higher concentrations of particulate matter is associated with an increase in COPD prevalence and a decline in patient respiratory function. This data is useful to healthcare practitioners looking for patient populations with high prevalence of COPD looking to make an impact in patient outcomes.[14]

A meta analysis of randomized controlled trials comparing procalcitonin-based protocols for continuing or discontinuing antibiotics versus the standard of care for acute exacerbations in COPD was conducted by researchers to evaluate the efficacy of procalcitonin based protocols.[15] Eight trials containing 1062 patients with acute exacerbations revealed procalcitonin-based protocols decreased antibiotic prescription (0.56, 95% CI (0.43 - 0.73)) and total antibiotic exposure (-3.83, 95% CI (-4.32 - -3.35)) without affecting clinical outcomes. Clinical outcomes reviewed during this meta-analysis include treatment failure, length of hospitalization, exacerbation recurrence rate, and mortality.[15] The small study populations used in this review sacrifices validity and may reduce the quality of evidence.[15]

Diagnosis, Assessment and Treatment

COPD is characterized by respiratory symptoms and airflow limitation resulting from exposure to toxic particulates. Inhaled particles cause oxidative stress which triggers the inflammatory response, leading to an imbalance in proteinases and antiproteinases. These enzymes are important to the body's repair process used in the lungs. Physiological changes that occur as a result of this imbalance and subsequent inability to repair damage include mucus hypersecretion, airflow limitation, the destruction of lung parenchyma, and hyperinflation.[16] The net effect of these changes is a decrease in the ability of the lungs to remain open during expiration and an inability to supply the blood with oxygen.

Spirometry values are used to diagnose and categorize COPD. Values used in the measurement of airflow limitation include forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1). A patient's FVC is the volume of air exhaled from the point of maximal inspiration. FEV_1 is the volume of air exhaled during the first second of performing an FVC.[2] The ratio of these values is recorded as FEV_1/FVC, and a post-bronchodilator score FEV_1/FVC of <0.70 indicates airflow limitation that is not completely reversible. This helps confirm a diagnosis of COPD in patients with other symptoms and exposure to toxic particulates.[16,17] Common symptoms of COPD include shortness of breath, chronic cough, and sputum production, and risk factors for COPD include tobacco use, occupational hazards, or exposure to other pollutants. Airflow severity is used to classify COPD and is based on a patient's post-bronchodilator FEV_1. Mild COPD is classified as GOLD 1 and indicates an FEV_1 of 80% of the predicted value. Moderate COPD is classified as GOLD 2 and indicates an FEV_1 between 50-80% of the predicted value. Severe COPD is classified as GOLD 3
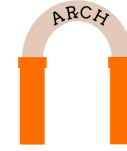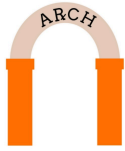
and indicates an FEV_1 between 30-50% of the predicted value. Very severe COPD is classified as GOLD 4 and indicates an FEV_1 of <30% of the predicted value.[17]

COPD symptoms are commonly assessed by two different methods. The Modified British Medical Research Council (mMRC) Questionnaire is used to evaluate the degree of a patient's breathlessness. The mMRC scale begins at Grade 0 and ends at Grade 4. Grade 0 is characterized by a patient who is only breathless with strenuous exercise. Grade 4 is characterized by a patient who is too breathless to leave the house, dress, or undress themselves. A more comprehensive assessment can be performed using the COPD Assessment Test (CAT). The CAT evaluates a patient's symptomatic burden resulting from COPD and should be used every 2-3 months to assess trends in a patient's COPD. This test is available at www.catestonline.org. Scores <10 are uncommon in patients diagnosed with COPD and scores ≥10 are uncommon in healthy patients.[17]

In order to fulfill a complete understanding of a patient's COPD, it is necessary to combine these assessment tools and evaluate a patient's "ABCD" rating. These values are determined by a patient's spirometry grade, either mMRC or CAT, and history of exacerbations. Patient's are categorized into group A, B, C, or D, with A indicating a lesser symptom burden and risk of exacerbation *(See Table 1)*. This assessment tool is then used to determine the appropriate therapy for each patient. Patients classified as Group A should begin treatment with a bronchodilator and either continue or attempt a new bronchodilator depending upon the outcome of therapy.

Bronchodilators that have proved to be effective treatment agents include short and long-acting beta2-agonists (SABA, LABA) and short and long acting muscarinic antagonists (SAMA, LAMA). Patients classified as Group B should begin treatment with a LABA or LAMA.[17] If symptoms persist, Group B patients may begin a combination of LAMA and LABA therapy.[17] Group C patients should begin therapy with a LAMA and proceed to either a LAMA/LABA combination or LABA/ICS combination if they experience further exacerbations.[17] Group D patients should begin therapy with either a LAMA or a LABA and an inhaled corticosteroid (ICS).[17] If symptoms persist, these patients should be treated with LABA/LAMA combination therapy, and then LABA/LAMA/ICS therapy if symptoms persist further.[17] If this triple therapy does not provide appropriate relief to a Group D patient, prescribers can consider one of two options: Roflumilast may be used in these patients who have an FEV_1 <50% of the predicted value and chronic bronchitis. This recommendation is based on new data on the effects of roflumilast in patients with COPD.[18] Macrolides may be considered if the patient is a former smoker (See Table 2).

Pharmacotherapy

Common bronchodilators used in the management of COPD include beta2-agonists. Their effect is carried out by action on beta2-adrenergic receptors which increase cyclic AMP and inhibit bronchoconstriction.[19] Short acting beta2-agonists (SABAs) provide relaxation of airway smooth muscle for approximately 4-6 hours while the effect of LABAs lasts for approximately 12 hours.[17] Commonly used

SABAs include levalbuterol and albuterol. Patients should be aware that SABAs may be associated with an accelerated heart rate after administration. It is also important to counsel patients on proper usage and storage of their SABAs.[20] Commonly used LABAs include formoterol and salmeterol, which are also associated with a rapid heart rate. Patients should be counseled on the appropriate use and storage of their LABA.[20]

LAMAs facilitate the inhibition of acetylcholine on M3 muscarinic receptors to block bronchoconstriction in airway smooth muscle.[19,20] Common LAMAs used in the treatment of COPD include aclidinium bromide and tiotropium, which have a duration of effect between 12 and 24 hours. Patients should be made aware that these drugs are associated with trouble urinating, dry mouth, and upset stomach.

ICSs are only recommended for use in COPD with other long-acting bronchodilator therapy.[17] ICSs inhibit the release of inflammatory mediators and mitigate IgE synthesis. This reduces the lungs response to allergens, but these medications do not have any bronchodilatory properties. Common ICSs used in combination with bronchodilators include budesonide, mometasone, and fluticasone. ICS may take several hours or days to notice an effect. Patients should be warned not to discontinue ICS use on their own, as some studies have shown an increase in exacerbations upon discontinuation of an ICS.[17] ICSs are associated with an increased prevalence of oral candidiasis, and patients should be counseled to rinse out their mouths and spit out the water after administration of these medications. Other adverse effects of ICS use include increased prevalence of pneumonia, GI upset and cataract development.[17,19,20]

Roflumilast is only recommended for use in patients with COPD who are Group D and have progressed through triple therapy with LAMA, LABA and ICS. These patients must also exhibit an FEV_1 that is <50% of the predicted value.[17] To treat COPD, roflumilast is dosed at 250 mcg once daily for 4 weeks and increased to a dose of 500 mcg once daily depending upon the patient's response. This medication has no bronchodilatory properties. Roflumilast has been known to cause GI upset, headaches, and muscle cramps, and patients should be made aware that this drug may be taken with or without food.[19,20]

A revised look at studies on continuous antibiotic use in patients with COPD suggests that their use may reduce exacerbation rates.[17] This is reflected in the recommendation to begin macrolides in patients who are former smokers and who have attempted triple therapy with LABA, LAMA, and ICS without relief. Azithromycin 250 mg/day or 500 mg three times per week and erythromycin 500 mg two times per week showed a reduction in exacerbations in patients treated with these therapies for one year.[17] Macrolides inhibit protein synthesis by binding the 50S subunit of bacterial ribosomes.[19,20] The most common side effect associated with these medications is GI upset including diarrhea, nausea and vomiting. Patients should also be counseled to look for symptoms including a rapid heartbeat, changes in hearing, and dizziness. These drugs should be taken with food if the patient is experiencing GI upset, and patients should be aware that the use of
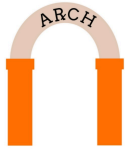
antacids two hours before or two hours after is not recommended *(See Table 3).*

Revisions and new information included in the updated GOLD 2018 Report will allow healthcare practitioners to use the most updated information in the care for COPD patients. By exploring this novel research and reviewing how these changes have been incorporated into current guidelines on COPD pathophysiology, diagnosis, treatment, and evaluation, individuals may be better equipped to manage patients with COPD.

Appendix

Table 1 - ABCD Rating		
Exacerbations	mMRC 0 - 1 or CAT < 10	mMRC ≥ 2 or CAT ≥ 10
0 or 1 which did not lead to hospitalization	Group A	Group B
≥ 2 or ≥ 1 which lead to hospitalization	Group C	Group D

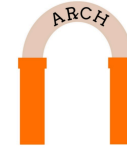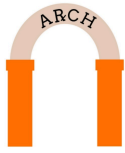| Table 2 - COPD Severity and Therapy				
Severity:	First-line:	Second-line:	Third-line:	Last-line:
Group A	SABA or SAMA or LABA or LAMA	Alternate bronchodilator		
Group B	LABA or LAMA	LABA and LAMA		
Group C	LAMA	LABA and LAMA	LABA and ICS	
Group D	LAMA or LABA and ICS	LAMA and LABA	LAMA, LABA and ICS	Roflumilast or macrolides

Table 3 - Pharmacotherapy							
	SABA	**SAMA**	**LABA**	**LAMA**	**ICS**	**Roflumilast**	**Macrolides**
Classification	Short Acting Beta$_2$ adrenergic Agonist	Short Acting Muscarinic Antagonist	Beta$_2$ adrenergic agonist	Long Acting Muscarinic Antagonist	Inhaled Corticosteroid	Phosphodiesterase-4 (PDE-4) Enzyme Inhibitor	Antibiotic
Mechanism of action	Activating beta$_2$ adrenergic receptors relaxes bronchial smooth muscle by activating cAMP.	Blocking muscarinic receptors causes bronchodilation by decreasing cGMP.\n\nNot selective for specific muscarinic receptors	Activating beta$_2$ adrenergic receptors relaxes bronchial smooth muscle by activating cAMP.\n\nHighly lipophilic resulting in long duration of action	Blocking muscarinic receptors causes bronchodilation by decreasing cGMP\n\nAntagonizes M$_1$, M$_2$, and M$_3$ muscarinic receptors	Glucocorticoids inhibit the activity of inflammatory mediators	Inhibition of PDE-4 causes an increase in cAMP in inflammatory cells suppressing cytokine release.	Binds the 50S ribosomal subunit and inhibits RNA dependent protein synthesis.
Side-effects	Accelerated heart rate, hypokalemia	Bronchitis	Chest pain	Xerostomia, upper respiratory tract infections, pharyngitis, sinusitis	Respiratory infections, rhinitis, candidiasis	Headache, weight loss, diarrhea	Loose stools, vomiting, diarrhea, skin photosensitivity,
Products	Albuterol, levalbuterol	Ipratropium bromide	Formoterol, salmeterol	Tiotropium	Budesonide, beclomethasone, mometasone, fluticasone	Roflumilast	Azithromycin, erythromycin
Evidence	21	22, 23	24, 25, 26	27, 28, 29, 30	31, 32	18, 33, 34, 35, 36	10, 37

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University of Findlay
College of Pharmacy