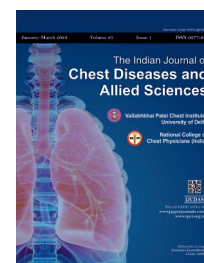


GOLD Strategy Update 2023: Rationale and Clinical Implications in Indian Perspective

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ABSTRACT

Chronic obstructive lung disease (COPD) is a major contributor to global disease burden with a huge socioeconomic impact. Global initiative for chronic obstructive lung disease (GOLD) strategy update 2023 is a step forward in the direction of evidence-based practice. Key topics like taxonomic classification, ABE grouping, single inhaler triple therapy, correct use of inhalers, etc. would have a positive impact on documentation and prescription practices in COPD management. The tobacco consumption habits are peculiar in India. There is a variation in prevalence estimates across diverse cultures. Non-smoking risk factors are important in Indian subcontinent especially in female and younger populations. We discuss the rationale of latest GOLD strategy update, its implications, and challenges in the management of COPD in Indian context.

Keywords: ABE grouping, Chronic obstructive lung disease, Global initiative for chronic obstructive lung disease 2023.

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ABBREVIATIONS USED IN THIS ARTICLE

ACO = Asthma–chronic obstructive lung disease overlap; BODE = Body mass index, obstruction, dyspnea, exercise performance; COPD = Chronic obstructive lung disease; FEV1 = Forced expiratory volume in the first second; DOSE = Dyspnea, obstruction, smoking, exacerbation; DPI = Dry powder inhaler; FVC = Forced vital capacity; GOLD = Global initiative for chronic obstructive lung disease; ICS = Inhaled corticosteroids; LABA = Long-acting beta agonists; LAMA = Long-acting muscarinic antagonists; LMICs = Low and middle income countries; NSCOPD = Non-smoking COPD; PM = Particulate matter; PRISm = Preserved ratio impaired spirometry; SITT = Single inhaler triple therapy; TB = Tuberculosis; WHO = World Health Organization.

INTRODUCTION

The global initiative for chronic obstructive lung disease (GOLD) 2023 strategy report brings forth major changes in diagnosis and treatment of disease per se and its exacerbations. A total of 387 new references have been added in an attempt to promote evidence-based practice. Summary of key changes is discussed in [Table 1](#).

PREVALENCE AND EPIDEMIOLOGY

Chronic obstructive lung disease (COPD) remains the top three causes of mortality worldwide especially in low and middle income countries (LMICs). The estimated prevalence of COPD is 10.3% globally [95% confidence interval (CI) 8.2%, 12.8%]. Generally, tobacco smoking is considered sine-qua-non for COPD, but it is high time we realize that non-smoking factors are equally important and contribute to >50% global burden of COPD especially in female and younger age groups. About 3 billion people use biomass and coal for cooking purposes worldwide. Workplace exposures, household pollution, and childhood disadvantage factors like chronic

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respiratory infections, low birth weight etc. are key determinants of lung function in adult life. The role of genomics needs to be explored further. The only gene best documented and implicated in COPD is alpha-1 anti-trypsin gene (*SERPINA-1*). Recent evidence has substantiated that E-cigarettes are harmful.¹

DEFINITION AND CLASSIFICATION

In GOLD 2023 document, a new definition for COPD along with new classification based on etiotypes has been proposed. Chronic obstructive lung disease has been termed a heterogeneous lung condition characterized by chronic respiratory symptoms like dyspnea, cough, sputum production, exacerbations due to abnormality of airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction. A recent taxonomic classification highlights that clinician should be aware of a wide range of non-smoking risk

Table 1: Keys changes in GOLD-2023 strategy update

1.	New definition of COPD and exacerbation proposed.
2.	Etiological classification of COPD; etiotypes proposed.
3.	PRISm concept introduced.
4.	Initial assessment changed from ABCD to ABE groups.
5.	Dual bronchodilation is preferred therapy over monotherapy as initial management. Triple therapy reserved for frequent exacerbators with high eosinophil counts and hospitalization.
6.	New set of parameters to assess severity of exacerbation of COPD.
7.	Emerging role of CT discussed.
8.	Evidence regarding mortality benefit for pharmacotherapy and non-pharmacotherapy updated. Data on vaccination updated.
9.	Information on comorbidities in COPD updated with addition of some conditions like frailty, polycythemia, and poor oral hygiene.
10.	Basic principles of inhaler therapy discussed and issues of non-adherence addressed.

COPD, chronic obstructive pulmonary disease; CT, computed tomography; GOLD, global initiative for chronic obstructive lung disease 2023; PRISm, preserved ratio impaired spirometry

factors especially while eliciting history and planning intervention. However, it should be acknowledged that COPD is not a monolithic disease and taxonomy holds little relevance in terms of management in practical settings. The definition of exacerbation has been updated by adding duration of 2 weeks for deterioration in symptoms in GOLD 2023.

DIAGNOSIS OF COPD

Forced spirometry remains the gold standard to diagnose COPD; post-bronchodilator forced expiratory volume in the first second/forced vital capacity (FEV₁/FVC) <0.70 is taken as cut-off to label an individual as COPD patient. Impulse oscillometry is a more sensitive tool than spirometry for early detection of small airway disease, but awaits validation by research trials. Precursor conditions such as pre-COPD, preserved ratio impaired spirometry (PRISm), and early COPD define subset of individuals who are symptomatic with evidence of structural (like emphysema) and/or physiological abnormalities (gas trapping, hyperinflation etc.) but do not fulfill spirometric criteria for COPD. For example, individuals with PRISm phenotype have preserved ratio but impaired spirometry; FEV₁/FVC <80% after bronchodilation. The prevalence ranges from 7.1% to 20.3% and disease course is variable. Further, the GOLD 2023 strategy is silent about whether to treat such patients or not. Screening of such conditions will open new opportunities to detect disease early and will shift the focus from cure toward prevention. However, more research is required to understand the underlying pathophysiology and deduce conclusions regarding management.

ASSESSMENT OF COPD

The initial assessment of COPD has been changed from ABCD grouping to ABE group. Groups C and D have been clubbed considering clinical relevance of exacerbations in the natural history of disease and prognosis rather than just symptoms which could be subjective. Also group C represented miniscule proportion (2–4%) adding little to the management decisions. Questionnaires

like COPD assessment test, chronic respiratory questionnaire, and composite scores body mass index, airflow obstruction dyspnea, exercise performance; the body mass index, obstruction, dyspnea, exercise performance. BODE index, dyspnea, obstruction, smoking, exacerbation; the dyspnea, obstruction, smoking, exacerbation. DOSE index provide holistic preview of social, emotional, and functional disabilities and should be added to daily practice. For objective measurement of lung function, spirometry remains the test of choice for diagnosis and follow-up. Self-monitoring via peak expiratory flow meter is not recommended in COPD unlike asthma. Chest radiograph is primarily used to rule out alternative diagnosis and comorbidities. Lately, computed tomography of thorax has become a popular tool impacting diagnostic and management decisions. Reasons could be manifold such as increased availability, recent lowering of age for lung cancer screening to 50 years, and advent of endobronchial valve therapy for emphysema. Other tests such as body plethysmography, diffusing capacity for carbon monoxide, and pulse oximetry can be utilized if available, but they are not essential. Absolute eosinophil count remains the sole marker to identify COPD in patients at higher risk of exacerbations. Eosinophil count more than 300 cells/microliter suggests inclusion of inhaled steroids in therapy and counts less than 100 dissuade use but 100–300 cells/microliter remains the gray area left to physician's discretion. There has been growing interest in identification of affordable diagnostic and prognostic biomarkers for COPD; however, data have failed to produce consistent results. New set of criteria have been added to assess severity of exacerbations in the present study.

PHARMACOLOGICAL MANAGEMENT

For initial management, the GOLD 2023 recommends any of long-acting bronchodilator agents, long-acting muscarinic antagonists (LAMA), or long-acting beta agonists (LABA) for group A patients, LABA/LAMA combination for group B, and triple therapy (LABA/LAMA with inhaled corticosteroids; LABA/LAMA/ICS) for category E patients preferably through single inhaler. Inhaled corticosteroids should be included in initial therapy only if there are frequent exacerbations, hospitalization, higher eosinophil counts (>300 cells/microliter), and history of concomitant asthma. If patient condition worsens/exacerbates even on triple therapy, other options like roflumilast (in FEV₁ < 50% and chronic bronchitis) and macrolide (in not current smokers) may be considered. Methylxanthines have modest benefit in stable COPD. Role of statins and leukotriene modifiers need to be explored further. The document also provides latest data on mortality benefit of various therapeutic options.

Review of literature indicated overuse of ICS in COPD leads to increased risk of undesirable outcomes like osteoporosis, pneumonia etc. especially in frail and elderly population with several comorbidities.² Therefore, expert consensus is that ICS/LABA is not preferred in COPD, unlike asthma. If there is indication for ICS, triple therapy is superior to ICS/LABA combination (IMPACT and ETHOS trials). When blood eosinophils fall and exacerbations cease to be frequent, therapy should be switched to bronchodilators (Conditional recommendation, European Respiratory Society; ERS 2020).²

There are certain areas that need attention. One of the reasons for overuse of solo ICS inhalers could be attributed to its wider availability. New inhalers preferably dry powder inhalers (DPIs) should be launched which adhere to guideline-based combinations. Long-acting muscarinic antagonists are more effective than LABA with favorable tolerability profile. Also, long-term use of LABA

monotherapy is related to cardiotoxicity, aggravation of hypoxemia, and tolerance issues. Recently, it has been withdrawn from the management of asthma patients.³ Therefore, in view of above, the continuation with LABA monotherapy in COPD may need further consideration. Biologic therapies like benralizumab may have a role in treating patients with COPD and concomitant asthma. The management of exacerbation remained largely similar to previous guidelines. There is no role of magnesium sulfate in acute exacerbation of COPD.

NON-PHARMACOLOGICAL MANAGEMENT

Vaccination data have been updated with addition of Zoster vaccine for patients with COPD over 50 years beside influenza, coronavirus disease, and pneumococcal and pertussis vaccines. Pulmonary rehabilitation decreases morbidity, but education alone and telehealth demonstrated no benefit. However, telerehab still holds relevance in patients who cannot show up. In patients with chronic mucus production, oscillatory positive expiratory pressure therapy is proven to be useful. Antitussives or mucolytics like recombinant deoxyribonuclease have not shown benefit. Cystic fibrosis transmembrane conductance regulator potentiator (icentofator), has also shown promising results. In the 2023 document, new bronchoscopic interventions have been proposed such as liquid nitrogen metered cryospray, rheoplasty, and targeted lung denervation which need to be evaluated further.

Incorrect use of inhalers and low compliance rates are important predictors of worse outcomes in patients with COPD. Self-reported non-adherence rates varies between 46 and 93% in LMICs. Basic principles of ICS therapy, choice of inhalers, and adherence issues have been discussed in detail in the latest document.

INDIAN PERSPECTIVE

In India, COPD is the second leading cause of disability adjusted life years and mortality with estimated burden ranging from 25.1 to 49.2 million. Meta-analysis by Daniel et al. reported the pooled prevalence ($n = 8659$) of 7.4%; higher in male (11.4%) as compared to female population (7.4%). It was higher in urban areas (11%) as compared to rural areas (5.6%). There is variation across regions and cultures; 19.3% in northern India and 7.4% in the southern part.⁴ Data from developed countries showed no gender-wise variation in prevalence.

It must be understood that prevalence estimates from India are not entirely accurate given the paucity of data and ambiguity of spirometric criteria used in the majority of studies. Also, spirometry is underused. Regan et al. reported that spirometry missed diagnosis in 42.3% of smokers with clinical or radiologic disease.⁵ Also, composite scores like BOLD and DOSE are not yet validated in the Indian population. Moreover, data so far are primarily focused on cigarette smoking. But in India, tobacco consumption is largely through *hookah*, *bidi*, and *chillum*. The prevalence of non-smoking COPD (NSCOPD) is high, especially in rural areas. A recent study from Uttar Pradesh showed that 56.5% of patients with COPD were non-smokers.⁶ Childhood respiratory infections, old treated tuberculosis (TB), and poorly treated asthmatics are other relevant risk factors relevant in Indian context. As per the World Health Organization (WHO) estimates 2019, India is the fifth most polluted country with 21 out of the 30 most polluted cities in India exceeding the WHO threshold of particulate matter ($PM_{2.5}$) emissions by 500%. Major contributors of air pollution are biomass fuel exposure (90% rural households, 32% urban households), road dust and road traffic

$PM_{2.5}$ emissions, crop residue burning, garbage burning, and brick kilns besides industrial pollution.^{7,8} Poor socioeconomic status, overcrowding, poor nutrition (maternal and child), in utero nicotine exposure, impoverished gut health, recurrent childhood infections etc. also linked to stunted lung health and may develop COPD later in life.⁹ Such factors are particularly relevant in LMICs like India. So, the actual burden of pre-COPD needs to be ascertained to plan preventive interventions well in time.

The first step is raising awareness about disease in public. Chronic obstructive lung disease is poorly recognized in India. A recent survey from Pune showed awareness rates of <1%.¹⁰ Moreover, spirometric diagnosis of COPD is dismal (chest physicians 46.9%, general physicians 21.7%) especially in primary care centers. The reasons could be many: non-availability of equipment, cost issues, lack of trained technicians, busy schedule of doctors, and lack of knowledge to interpret the report.¹¹ Besides, addressing availability and cost issues, spirometry training programs need to be conducted regularly even for general physicians.

The prevalence and healthcare utilization is high in groups B and D in India (prevalence estimates up to 27% and 42% respectively).¹² Another study revealed that 80% of smokers belonged to group D and 57% of the non-smokers were in group B.¹³ The latest ABE grouping is not only easy to remember but also more clinically relevant in Indian context. This would encourage proper documentation among physicians in field settings.

Some findings such as underuse of inhalers, overuse of ICS, suboptimal treatment, and inhaler prescriptions not aligned to GOLD recommendations are similar in Indian and Western populations.¹² Overall, ICS-LABA has been found to be the most prescribed maintenance therapy. Single inhaler triple therapy (SITT) is effective in reducing moderate-severe exacerbations with better compliance rates in accordance with western data; however, its role in NSCOPD and asthma-COPD overlap (ACO) populations remain to be established.^{12,14} However, there is no direct evidence of effectiveness of triple therapy in population subsets with high eosinophil counts like ACO and NSCOPD. The prevalence of ACO is 21–27%, while that of NSCOPD is 65%. Moreover, Indian patients may have elevated mean blood eosinophils due to an increased rate of parasitic infections. Threshold values for blood eosinophil count in the Indian population need to be evaluated.¹²

Public, physicians, and policymakers should join hands to tackle this menace. Chronic obstructive lung disease prevention should be the target. The Ministry of Environment, Forest and Climate Change, Government of India, has taken several policy measures to mitigate pollution such as adoption of compressed natural gas, odd-even measures in Delhi, Pradhan Mantri Ujjwala Yojana, National Clean Air Program, National Green Corps Program, introduction of Bharat Stage VI vehicle and fuel standards, electric vehicles, installation of online continuous emission monitoring systems, usage of LPG for cooking purposes, door-to-door collection of segregated waste, and installation of compost pits in urban areas. Maintenance of 33% green cover around urban areas and installation of water fountains across cities are adopted to control concentration of PM and dust particles. National ambient air quality standards are developed by the Central Pollution Control Board. Air Pollution Day is observed on December 6 to raise public awareness.^{8,15} SAMEER App has been launched to provide air quality information to public along with option of registering complaints against air-polluting activities.¹⁶ These means should impact the COPD prevalence in the country provided the implementation and monitoring is ensured by the concerned agencies.

Table 2: Take-home message

<i>Take home message</i>	
<i>What we should know</i>	<i>What we need to work upon</i>
1. COPD is preventable and treatable but not curable	1. Estimating exact prevalence of COPD and pre-COPD through field surveys
2. COPD is not a monolithic disease	2. Objective assessment of biomass fuel exposure and implication in lung health
3. Smoking is not sine-qua-non for COPD	3. More surveys to estimate burden of tuberculosis-associated COPD
4. Forced spirometry alone is not 100% sensitive for diagnosis of COPD	4. Role of genomics in COPD
5. COPD is underestimated, underdiagnosed, and misdiagnosed	5. Implementation of guidelines at primary level
6. ICS should be used cautiously in COPD	6. Spreading awareness about disease and promote correct use of prescribed therapy
7. Proper documentation on prescription slip is a must	

Similarly, medical fraternity observe World COPD day on third Wednesday of November every year. However, educational activities like quiz competition, skits, poster presentation etc. should not be limited to medical institutions only. Teens in schools and non-medical colleges too should be educated about COPD particularly harmful effects of electronic delivery devices/vaping. Certain indigenous online platforms/websites can be created where COPD patients and caregivers can share their struggle of COPD. Chronic obstructive lung disease camps should be organized on lines of non-communicable diseases like diabetes. Upscaling of such activities will not only dispel myths but also sensitize policy makers to upgrade funding.

Clinicians should be aware of non-smoking risk factors and precursor conditions. Spirometric-based diagnosis and correct labeling of patients is non-negotiable. Chronic obstructive lung disease should be taught as a separate topic under competency-based curriculum at undergraduate level. Evidence-based practice at primary level should be ensured by regular sensitization of physicians at primary level via educational activities like seminars, workshops, online trainings etc. Counseling of patients is pertinent because societal pressures and stigma related to inhaler use eventually impedes successful management of patients. Non-adherence to COPD therapy needs to be addressed through proper education and counseling. Inhaled bronchodilators and forced spirometry tests should be made available at primary health centers.

Smoking cessation remains the cornerstone intervention. Non-government organizations and primary healthcare centers can be pooled to run smoking cessation clinics for wider reach. Other preventive strategies include proper prenatal care, staying active, limiting toxic exposures, maintaining good nutrition, etc. The latest theme (Your Lungs for Life) of 21st World COPD day celebrated on November 16, 2022, echoed the same idea.¹⁷ Under use of vaccination should be addressed. Taxonomic classification calls for more individualized approach. A recent meta-analysis showed pooled prevalence of COPD of 7% in population above 30 years of age.¹⁸ Salvi et al. reported that it ranged from 0.1% to 0.9% in age groups between 5 and 29 years.¹⁹ National control programs for TB and human immunodeficiency virus can be utilized to screen for COPD by incorporating spirometry on follow-up.

Nation can no longer ignore the need for COPD prevention and control program. National COPD action plan should be formulated. Chronic obstructive lung disease guidelines should be updated

which is validated in Indian population and tailored to our needs. Chronic obstructive lung disease registries should be maintained. Smart phones can be utilized to demonstrate inhaler technique and monitor compliance.

Areas for future research include updating prevalence estimates using uniform criteria, validation of composite scores, development of cost-effective diagnostic tools/biomarkers, and interventions. [Table 2](#) depicts the take-home message.

CONCLUSION

Chronic obstructive lung disease is a major killer worldwide with a huge socioeconomic impact especially in LMICs like India. The GOLD strategy update 2023 is a step forward in direction of evidence-based practice. Key topics like taxonomic classification, ABE grouping, SITT, correct use of inhalers etc. would have a positive impact in documentation and prescription practices in COPD management. India needs more surveys to find the exact prevalence of COPD and pre-COPD, and to upgrade its guidelines to address local needs/issues. Implementation and dissemination of latest practices in the primary care settings is imperative to tackle this menace. India needs a COPD prevention and control program on the lines of national TB elimination program and national AIDS control program.

REFERENCES

- 2023 GOLD Report - Global Initiative for Chronic Obstructive Lung Disease - GOLD Available from: <https://goldcopd.org/2023-gold-report-2/>.
- Chalmers JD, Laska IF, Franssen FME, et al. Withdrawal of inhaled corticosteroids in COPD: A European respiratory society guideline. *Eur Respir J* 2020;55(6):2000351. DOI: 10.1183/13993003.00351-2020.
- Global initiative for asthma. Global strategy for asthma management and prevention, 2022. Available from: <https://ginasthma.org/>.
- Daniel R, Aggarwal P, Kalaivani M, et al. Prevalence of chronic obstructive pulmonary disease in India: A systematic review and meta-analysis. *Lung India* 2021;38(6):506. DOI: 10.4103/lungindia.lungindia_159_21.
- Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and radiologic disease in smokers with normal spirometry. *JAMA Intern Med* 2015;175(9):1539. DOI: 10.1001/jamainternmed.2015.2735.
- Mahmood T, Singh RK, Kant S, et al. Prevalence and etiological profile of chronic obstructive pulmonary disease in nonsmokers. *Lung India* 2017;34(2):122. DOI: 10.4103/0970-2113.201298.

7. Gurjar BR, Ravindra K, Nagpure AS. Air pollution trends over Indian megacities and their local-to-global implications. *Atmos Environ* 2016;142:475–495. DOI: 10.1016/j.atmosenv.2016.06.030.
8. Sharma D, Mauzerall D. Analysis of Air Pollution Data in India between 2015 and 2019. *Aerosol Air Qual Res.* 2022;22(2):210204.
9. Duan P, Wang Y, Lin R, et al. Impact of early life exposures on COPD in adulthood: A systematic review and meta-analysis. *Respirology* 2021;26(12):1131–1151. DOI: 10.1111/resp.14144.
10. Ghorpade DD, Raghupathy A, Londhe JD, et al. COPD awareness in the urban slums and rural areas around Pune city in India. *NPJ Prim Care Respir Med* 2021;31(1):6. DOI: 10.1038/s41533-021-00220-4.
11. Vanjare N, Chhowala S, Madas S, et al. Use of spirometry among chest physicians and primary care physicians in India. *Prim Care Resp Med* 2016;26:16036. DOI: 10.1038/npjpcrm.2016.36.
12. Dhar R, Talwar D, Salvi S, et al. Use of single-inhaler triple therapy in the management of obstructive airway disease: Indian medical experts' review. *ERJ Open Res* 2022;8(1):1–17. DOI: 10.1183/23120541.00556-2021.
13. Bajpai J, Kant S, Bajaj D, et al. Clinical, demographic and radiological profile of smoker COPD versus nonsmoker COPD patients at a tertiary care center in North India. *J Fam Med Prim Care* 2019;8(7):2364. DOI: 10.4103/jfmpc.jfmpc_347_19.
14. Salvi S, Balki A, Krishnamurthy S, et al. Efficacy and safety of single-inhaler triple therapy of glycopyrronium, formoterol and fluticasone in patients with COPD: A double-blind, randomised controlled trial. *ERJ Open Res* 2021;7(3):1–9. DOI: 10.1183/23120541.00255-2021.
15. Ganguly T, Selvaraj KL, Guttikunda SK. National Clean Air Programme (NCAP) for Indian cities: Review and outlook of clean air action plans. *Atmos Environ X* 2020;8:100096. DOI: 10.1016/j.aeaoa.2020.100096.
16. CPCB asks NCR states pollution board and agencies to take immediate and effective steps to control Air Pollution. Available from: <https://pib.gov.in/Pressreleaseshare.aspx?PRID=1685103>.
17. World COPD Day - Your Lungs for Life: The Forum of International Respiratory Societies - Global Initiative for Asthma - GINA. Available from: <https://ginasthma.org/world-copd-day-your-lungs-for-life-the-forum-of-international-respiratory-societies/>.
18. Verma A, Gudi N, Yadav UN, et al. Prevalence of COPD among population above 30 years in India: A systematic review and meta-analysis. *J Glob Health* 2021;11:04038. DOI: 10.7189/jogh.11.04038.
19. Salvi S, Kumar GA, Dhaliwal RS, et al. The burden of chronic respiratory diseases and their heterogeneity across the states of India: The Global Burden of Disease Study 1990-2016. *Lancet Glob Heal* 2018;6(12):e1363–e1374. DOI: 10.1016/S2214-109X(18)30409-1.