Implications for Management of Chinese Patients with Chronic Obstructive Pulmonary Disease Based on the 2024 Italian Consensus on Triple Inhaled Therapy (Postprint)

Authors: Chen Chuping, Liu Lidi, Yang Ziyu, Zhang Peng, Zhang Rui, Yuan Bo, Shen Can, Yang Rong, Li Dongze, Liao Xiaoyang, Lei Yi, Lei Yi

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Abstract

In China, chronic obstructive pulmonary disease (COPD) is a common chronic illness characterized by high morbidity and mortality, imposing a substantial burden on both individual health and socioeconomic conditions. Pharmacotherapy constitutes the cornerstone of COPD patient management and should adhere to individualized principles, among which triple therapy (inhaled corticosteroids [ICS], long-acting muscarinic antagonists [LAMA], and long-acting $ $2-agonists [LABA]) has garnered considerable attention. In 2024, an Italian respiratory expert panel, through deliberations by a scientific committee and expert group, published the "Italian Consensus: Triple Inhaled Therapy for Chronic Obstructive Pulmonary Disease" to standardize COPD patient management. This article aims to interpret the core highlights regarding triple therapy presented in this consensus, with particular emphasis on analyzing the applicability of triple therapy across different clinical scenarios, thereby providing references for optimizing COPD drug selection in Chinese clinical practice, facilitating enhanced standardization of treatment, reducing therapeutic arbitrariness, and improving treatment outcomes.

Full Text

Implications for the Management of COPD Patients Based on the Italian Consensus in 2024: Triple Inhalation Therapy in Chronic Obstructive Pulmonary Disease

CHEN Chuping[1], LIU Lidi[1], YANG Ziyu[1], ZHANG Peng[1], ZHANG Rui[1], YUAN Bo[1], SHEN Can[1], YANG Rong[1], LI Dongze[2], LIAO Xiaoyang[1], LEI Yi[1]*

[1]Teaching & Research Section/General Practice Research Institute, General Practice Medical Center, West China Hospital, Sichuan University, Chengdu 610041, China
[2]Emergency Department, West China Hospital, Sichuan University, Chengdu 610041, China

Corresponding author: LEI Yi, Professor; Email: leiyi111@scu.edu.cn

Abstract

In China, chronic obstructive pulmonary disease (COPD) is a prevalent chronic disorder with high incidence and mortality, imposing substantial burdens on individual health and socioeconomic systems. Pharmacological treatment is central to COPD management and should follow personalized principles, with triple therapy combining inhaled corticosteroids (ICS), long-acting muscarinic antagonist (LAMA), and long-acting beta-agonist (LABA) gaining considerable attention. In 2024, an Italian respiratory expert panel published the "An Italian Delphi Consensus on the Triple Inhalation Therapy in Chronic Obstructive Pulmonary Disease" to standardize COPD patient management through scientific committee and expert panel deliberations. This article interprets the consensus' core points regarding triple therapy, focusing on its applicability across diverse clinical scenarios to provide evidence-based guidance for optimizing drug selection in Chinese COPD treatment, thereby improving treatment standardization, reducing therapeutic arbitrariness, and enhancing clinical outcomes.

Key words: Pulmonary disease, chronic obstructive; Triple therapy; Consensus; Disease management

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Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable chronic disease [1] that represents a leading cause of mortality and disability worldwide [2], imposing significant health and economic burdens. The World Health Organization identified COPD as the fourth leading cause of death globally in 2021, accounting for 5% of total deaths [3]. In Italy, COPD contributes to 55% of respiratory disease-related mortality [4]. The 2018 China Pulmonary Health Study reported a COPD prevalence of 8.6% among adults over 20 years of age in China [5]. Between 2020 and 2050, COPD is projected to cause $4.326 trillion in global economic losses, with China bearing the largest absolute burden at $1.363733 trillion, compared to Italy' s $255.42 trillion [6]. Given China' s aging population and vast demographic base, the COPD burden is expected to intensify, exerting profound impacts on individuals, families, and socioeconomic systems [7]. The importance of early prevention, accurate

diagnosis, and standardized treatment for COPD is self-evident, with primary healthcare institutions playing a critical role in identifying and managing early-stage cases.

COPD management emphasizes comprehensive treatment, yet pharmacotherapy remains central, requiring individualized treatment selection. Triple therapy—comprising inhaled corticosteroids (ICS), long-acting muscarinic antagonist (LAMA), and long-acting beta-agonist (LABA)—has attracted considerable attention. Recent clinical studies demonstrate that triple therapy offers significant advantages over ICS/LABA dual therapy in reducing exacerbation frequency, improving lung function, and decreasing all-cause mortality [8-9]. Triple therapy not only improves patients' daily quality of life but also helps reduce long-term healthcare costs when implemented at the optimal time [10]. Although the 2024 edition of the "Chinese Guidelines for Primary Diagnosis and Management of Chronic Obstructive Pulmonary Disease" (hereinafter referred to as the "Chinese Primary Care Guidelines") has incorporated recommendations on triple therapy, China still lacks authoritative guidelines specifically focused on COPD triple therapy, resulting in limited adoption and inconsistent disease management.

Italian respiratory medicine experts conducted a multi-center research project that produced the "2024 Italian Consensus on Triple Inhalation Therapy in Chronic Obstructive Pulmonary Disease" (hereinafter referred to as the "Consensus"). Developed by a scientific committee and expert panel using a modified Delphi method, the scientific committee conducted two Delphi rounds. The first round identified 11 items related to COPD management, and the second round converted these into statements for independent rating by the expert panel using a 9-point scale, with scores of 7 or above indicating consensus. If consensus was achieved in the initial rating, no further rounds were required. Following consensus, six experts drafted the manuscript, which was published in September 2024 in the official journal of the Italian Respiratory Society, *Multidisciplinary Respiratory Medicine*. While not all statements achieved unanimous consensus, the results provide valuable insights for clinical decision-making, helping physicians better understand COPD management. The Consensus targets internists, patients, primary care physicians, other healthcare professionals, and policymakers. Although it does not include formal evidence quality reporting or strength of recommendation assessments, it supports its positions based on the latest available evidence and expert ratings, offering Chinese clinicians a comprehensive perspective on refined diagnosis, treatment, and standardized management of COPD.

This article provides an in-depth analysis of the Consensus, exploring its potential value and implications for Chinese general practitioners and clinical practice in the context of China' s actual COPD diagnosis and management conditions.

1.1 Triple Inhalation Therapy

The Consensus focuses its discussion on triple therapy, particularly regarding the timing for upgrading from dual therapy to triple therapy, direct upgrade from single bronchodilator to triple therapy, and first-line triple therapy, with relevant summaries provided in Figure 1 [Figure 1: see original paper]. The Chinese Primary Care Guidelines reference GOLD report recommendations on triple therapy, emphasizing individualized treatment, consistent with the Italian Consensus. However, as China' s specific guidance on triple therapy requires further refinement, the Consensus' focus on timing for triple therapy can fill this gap and provide reference for Chinese practice.

1.2 Timing for Upgrading from Dual Therapy to Triple Therapy

In clinical practice, treatment regimens are adjusted based on patient response evaluation, primarily using stepwise therapy. The Consensus states that when patients adhering to dual therapy fail to achieve treatment goals (i.e., exacerbations occur despite dual bronchodilator therapy, or respiratory symptoms persist after ICS/LABA), treatment can be escalated to triple therapy. This recommendation applies to patients without comorbidities, particularly cardiovascular disease. Chinese studies have found that compared with ICS/LABA, both LAMA/LABA dual therapy and triple therapy significantly increase the risk of major adverse cardiovascular events, providing important reference for medication selection in COPD patients with cardiovascular comorbidities [11]. Guidelines from the United States, Canada, and the United Kingdom also propose indications for upgrading from dual to triple therapy (Table 1), with most emphasizing the importance of exacerbations or dyspnea in guiding this upgrade.

The FULFIL trial [12] demonstrated that after 24 weeks, patients on once-daily triple therapy experienced symptom relief, reduced exacerbation rates, and improved quality of life compared with dual therapy patients. A cohort study found that among patients with at least two exacerbations in the previous year, triple therapy significantly reduced exacerbation risk and other outcome risks compared with dual therapy, with risk reduction effects increasing with prior exacerbation frequency [13]. Although this study found similar pneumonia incidence between treatment groups, the mainstream view remains that triple therapy carries higher pneumonia risk than dual therapy [14-15], which does not warrant avoiding this regimen. For COPD patients with one or more exacerbations in the past year, a 23% reduction in exacerbation rate is considered to outweigh the 39% increase in pneumonia risk, as exacerbation events are far more common than pneumonia events in these patients [16]. Therefore, the Consensus emphasizes careful evaluation of the potential benefits of reducing exacerbations versus increasing infection events to achieve optimal personalized outcomes.

The Chinese Primary Care Guidelines also emphasize that peripheral blood

eosinophil (EOS) count has reference value for assessing whether patients need ICS. EOS count correlates with patient responsiveness to ICS, with higher EOS counts in COPD patients associated with reduced exacerbations following ICS treatment [17]. The KRONOS study suggested that even in moderate COPD patients without recent exacerbations, triple therapy may be considered if EOS count exceeds 100 cells/mm^{3} [18]. Post-hoc analysis of the ETHOS study [19] confirmed that when blood EOS counts range between 100-300 cells/mm^{3}, triple therapy still demonstrates benefits over LAMA/LABA dual therapy in reducing moderate or severe COPD exacerbation rates, improving symptoms and lung function, with benefits generally increasing with baseline EOS count. The relationship between EOS count and ICS responsiveness is continuous, with EOS playing an important predictive role in clinical treatment decisions. Additionally, blood EOS count may be a prognostic indicator for COPD patients during exacerbations. A retrospective study found that blood EOS count in acute exacerbation COPD (AECOPD) patients correlates with comorbidity occurrence, with elevated EOS potentially indicating reduced risk of cor pulmonale, respiratory failure, atrial fibrillation, and 3-year mortality [20], though further research is needed for confirmation.

1.3 Timing for Direct Upgrade from Single Bronchodilator to Triple Therapy

The Consensus proposes that in COPD treatment, when treatment goals are not achieved—such as deterioration or unmet patient-reported outcomes (PROs)—direct upgrade from single bronchodilator to triple therapy may be considered [4]. PROs are crucial for assessing symptoms, their impact on daily activities, and treatment response [24]. The most commonly used questionnaires and scales for evaluating PROs include the modified Medical Research Council (mMRC) dyspnea scale, COPD Assessment Test (CAT), Transition Dyspnea Index (TDI), and St. George' s Respiratory Questionnaire (SGRQ) [4]. The Chinese Primary Care Guidelines emphasize mMRC and CAT for symptom assessment due to their brevity, clarity, ease of use, and good reproducibility, making them suitable for outpatient or patient self-assessment. The Consensus proposes SGRQ, which is rigorous and detailed. Chinese studies have investigated its applicability and reference value in Chinese populations, finding that SGRQ scores correlate with lung function levels in COPD patients [25]. Although its comprehensive content requires more time, limiting clinical promotion and primarily restricting its use to academic research, SGRQ can serve as an effective tool for quantifying lung function impairment in COPD patients who cannot undergo spirometry due to multidimensional limitations, have absolute contraindications for pulmonary function testing, or receive care in community health centers without spirometry equipment [26], potentially reducing healthcare burden and offering clinicians a new direction for COPD patient management and evaluation.

GOLD recommends escalating or de-escalating therapy based on symptom deterioration or improvement and exacerbation severity. Current research primarily

focuses on indications for upgrading from dual to triple therapy or its benefits, with limited studies on direct upgrade from single bronchodilator to triple inhalation therapy. The Consensus expert panel endorses GOLD' s stepwise therapy approach but notes that for patients diagnosed late with significant lung function or physical activity decline, imaging abnormalities, or rapid disease progression, more aggressive treatment may improve symptoms and reduce mortality. However, further large-scale studies are needed to demonstrate the benefits of this approach and refine the strategy. It should be noted that both Chinese guidelines and the Italian Consensus emphasize individualized treatment for COPD triple therapy and recommend comprehensive multifactorial assessment to develop optimal treatment plans.

1.4 Timing for First-Line Triple Therapy

Current research and discussion on triple therapy application beyond strict indications or its consideration in non-recommended situations remain limited, with optimal timing for initiation still unclear. However, clinical practice has increasingly recognized that triple therapy is not limited to escalation from dual therapy but can also be considered as initial treatment. Studies have found that for moderate or severe COPD patients post-exacerbation, immediate triple therapy initiation is significantly associated with reduced exacerbations and lower healthcare costs compared with delayed initiation [27-28]. Additionally, initiating triple therapy within 30 days of a COPD exacerbation significantly reduces subsequent exacerbation risk (1.52 events/year), with each 30-day delay increasing exacerbation risk by 5% [29]. The Chinese Primary Care Guidelines state that when developing initial treatment plans for stable COPD patients, triple therapy may be considered for Group E patients (high risk: 2 exacerbations/year or 1 hospitalization/year with symptoms of any severity) with EOS 300/ L or comorbid asthma [21] (A, strong recommendation). The Italian Consensus recommends triple therapy as a first-line option for patients recently discharged from hospital or experiencing both dyspnea and deteriorating respiratory function during exacerbations, consistent with VANFLETEREN et al. [30].

The Italian Consensus provides detailed analysis of triple therapy applicability, offering valuable reference for Chinese clinicians. It provides recommendations on appropriate timing for initiating triple therapy while emphasizing comprehensive patient assessment, particularly balancing adverse events against therapeutic benefits. This facilitates disease burden reduction and supports physicians in better COPD patient management, representing an area where future clinicians must translate theory into practice.

However, China faces numerous challenges in triple therapy implementation. First, the complexity of inhaler devices and increased medication burden can reduce COPD patient adherence, underscoring the importance of patient management. Various inhalers are available, primarily single-inhaler triple therapy (SITT) and multiple-inhaler triple therapy (MITT), with patient preference guiding selection. Multiple studies confirm that SITT demonstrates better

adherence and persistence [31-32], suggesting that general practitioners should consider inhaler device selection to improve adherence and management outcomes. Second, community hospitals in China have low availability of triple therapy medications. A survey of medication availability in Chinese healthcare institutions found that current community health service centers have low availability rates for dual and triple therapy medications, at approximately 40% [33], failing to meet patient needs. Although this study had a small sample size limited to nine provinces, restricting generalizability, it highlights a current issue in Chinese community hospitals that requires promoting relevant medications into the national essential medicines list to improve availability and meet diverse needs.

Furthermore, Chinese primary care physicians' understanding and mastery of COPD remains concerning. Due to limited specialized knowledge, they may fail to recognize COPD patients in clinical practice, and non-standardized treatment may increase exacerbation risk. Therefore, it is essential to provide relevant training for primary care physicians and develop guidelines to enable more standardized and specialized COPD patient management.

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ORCID:
CHEN Chuping https://orcid.org/0009-0003-4242-2041
LEI Yi https://orcid.org/0000-0003-3197-5620

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Note: Figure translations are in progress. See original paper for figures.