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Twenty years of GOLD (1997-2017). The origins

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Background

On September 24-26, 1958, an international workshop of 50 first-class British chronic obstructive pulmonary disease (COPD) experts, also known as the ***CIBA Guest Symposium***, was organized to explore temporary definitions, classifications, and terminology, and suggest lines of research to potentially clarify uncertainties which at that time impede the formulation of a satisfactory system of classification [1]. This document was published to encourage professionals to use defined terms in making pathological, clinical, and functional assessments, to investigate the reproducibility of these assessments in the hands of observers, and to determine their significance and validity by comparing the results of the different types of assessment with one another.

Intriguingly, it took forty two years for the international respiratory community to implement and start new actions and initiatives. Of note that this amount of time was exactly identical to that spent by the British Royal Navy during the 18th century to begin to give out citrus fruit routinely to sailors for long distance sea travels to prevent and treat the life-threatening outbreaks of scurvy [2].This short historical anecdote may give us a general overview of the long-term healthcare battle against COPD during the 20th century.

Implementation

In the late 1990s, COPD was considered a major public health problem. It was the fourth leading cause of chronic morbidity and mortality in the United States (US) and was projected to rank fifth in 2020 as a worldwide burden of disease according to a study published by the World Bank/World Health Organization (WHO) [3]. Nevertheless, COPD failed to receive adequate attention from the health care community and

government officials [4]. With these concerns in mind, a committed group of experts lead by the late Romain Pauwels [5] – *'...as a community of people who care for and are interested in respiratory diseases, it is time that a major effort is focused on this disease...'* [6] –, encouraged the US National Heart, Lung, and Blood Institute (NHLBI) (Director, Claude Lenfant [7]) and the World Health Organization (WHO) (Director, Nikolai Khaltaev) to create and develop the ***Global Initiative for Chronic Obstructive Lung Disease***, better known as **GOLD**, a think tank that was developed and shaped by Suzanne S Hurd [8] (Figure 1). On one hand, Claude Lenfant had formerly served as NHLBI Division of Lung Diseases (DLD) Director between 1972 and 1980 and then as Director of the NHLBI, National Institutes of Health (NIH), between 1982 and 2003. His solid academic and scientific roots, formerly Professor of Medicine and Physiology and Biophysics at the University of Washington, Seattle, led him to the position of GOLD Executive Director from 2005 through 2015; on the other hand, Suzanne S Hurd began in 1997 her immense organizational activity as GOLD Scientific Director until the end of 2015. Formerly, she had served as Director of the DLD at the NIH from 1983 until 1999, after receiving her PhD degree from the University of Washington, Seattle. Suzanne S Hurd is a worldwide expert in development of programs for care of patients with asthma and COPD and was actually the GOLD kingpin during these 20 years.

GOLD's important goals were to increase awareness of COPD and help the thousands of patients who suffer from this disease and die prematurely from COPD or its complications. Accordingly, the first step in the GOLD program was to prepare a consensus *Workshop Report, Global Strategy for the Diagnosis, Management, and Prevention of COPD*. The appointed GOLD Expert Panel, integrated by a distinguished group of health professionals from the fields of respiratory medicine, epidemiology,

socioeconomics, public health, and health education, reviewed existing COPD guidelines, as well as new information on pathogenic mechanisms of COPD as they developed a consensus document (Figure 2). Many of the original recommendations required further additional studies and evaluations as the GOLD program was implemented and this is the principal core of GOLD. In the 1990s, a major drawback was the incomplete information about the causes and prevalence of COPD, especially in developing countries. While cigarette smoking was a major known risk factor, much remained to be learned about other causes of this disease.

The major objective stated and underlined in 2001 GOLD Report [3], was "*...to form an independent global network of individuals and organizations committed to increase awareness of COPD among health professionals, health authorities, and the general public; improve diagnosis, management and prevention; stimulate research; and, provide evidence-based educational resources concerning COPD for worldwide use. These goals had to be achieved in cooperation with professional health organizations, patient organizations and foundations, government agencies, health care providers and individuals with interest in COPD research, patient management, and health promotion and disease prevention*", that still prevails. It is of note to underline that GOLD is not strictly speaking a proper clinical guideline as the many produced quite legitimately by scientific societies all over the world and should not be read as such. The fundamental original idea behind GOLD is to provide a strategy for the diagnosis and the management of COPD resulting in a worldwide document and, for this reason alone, the GOLD documents cannot be regarded as a standard clinical guideline *per se*. It is considered impossible to make the same guidelines for all countries. If used to inspire

guidelines anywhere, it has to be expanded more locally paying particular attention to its specific geographic and socio-sanitary idiosyncrasies.

Organizational Network

GOLD was originally created as a non-governmental corporation, registered with the US tax office as a not-for-profit organization. A formal structural organization was developed with its own by-laws, a Board of Directors, a Scientific Committee, and two individuals – Executive Director, C Lenfant MD, PhD, and Science Director, SS Hurd PhD – until 2015, continued by Rebecca Decker, current GOLD and Global Initiative for Asthma (GINA) Program Director. The Board of Directors (Executive Committee) meets face-to-face once annually, whereas the Scientific Committee meets at the annual meetings of the *American Thoracic Society* (ATS) and the *European Respiratory Society* (ERS) meetings well attended by a solid worldwide network of GOLD National Leaders. The GOLD Strategy document is updated annually (GOLD Updates) and revised every 5 years (in 2006, 2011, and 2017) by the Scientific and Executive Committees (GOLD Revisions or Reports) from 2001 [3] (Figure 2). The committee is composed by members with highly academic expertise, whose composition and disclosures of interest are regularly posted on the website [9]. Yearly updates are published on the GOLD website without external revisions, at variance with the reports always sent to several external expert referees [10]. Executive GOLD Reports Summaries for 2001 [6], 2006 [11], and 2011 [12] have been sequentially published in the *American Journal of Respiratory and Critical Care Medicine* [13] alone, while the last GOLD 2017 Report has been also published in three other top journals such as *European Respiratory Journal* [14], *Respirology* [15], and *Archivos de Bronconeumologia* [16], hence involving the official Journals of the four major worldwide scientific respiratory societies (ATS, ERS,

the *Asian Pacific Society of Respirology* [APSR], and the *Asociación Latinoamericana de Tórax* [ALAT], respectively).

Reports and Updates

Figure 3 depicts the historical perspective of the principal GOLD documents (Reports and Updates) produced over the last 20 years [17] complemented by a more detailed illustration of the four main GOLD Revisions or Reports (Figure 4). In the GOLD 2001 Report [3], the use of four grades of evidence levels was assigned to statements, where appropriate was prominently featured into four grades (A, B, C, and D) to identify the assessed randomized controlled trials [RCTs]. It is of note that a novel classification of COPD severity based on several FEV_1 thresholds, including the presence or absence of chronic respiratory failure, was introduced for the first time together with key therapeutic recommendations. Note that, in addition to the four major GOLD categories (mild, moderate with two variants [a and b], and severe), there was a GOLD 0, "At Risk" stage, defined by the sole presence of chronic cough and sputum with normal spirometry, that offered a unique opportunity to identify individuals at risk for COPD consistent with increased awareness among health care providers. The 2001 classification of COPD severity proposed was uni-dimensional based on forced spirometry alone matched with therapy and management for patients with stable COPD. This classification is known worldwide as the *GOLD 1234*, a nickname that has proven to be (and still is) massively used by thousands generations of physicians to manage COPD patients on a daily basis.

In the second GOLD Report published in 2006 [11], the severity classification of COPD continued to be based on spirometric values alone, that essentially remained unchanged

(Figure 4). However, it is of note to highlight that GOLD 0 was no longer included, as there was incomplete evidence that the individuals who meet GOLD 0 necessarily progress on to GOLD 1. GOLD 0 was discarded due to data published from the *Copenhagen City Heart Study* cohort [18], in which less than 7% of men and women had GOLD 0 at baseline, with an overall prevalence of 6%. After 5 and 15 years, COPD developed in 13% and 21% of smokers with GOLD 0 at enrollment, respectively, although symptoms of cough and sputum were associated with an excess lung function decline, along with the FEV_1 reduction observed in asymptomatic unobstructed smokers. Consequently, it was believed that GOLD 0 was of little help in identifying subjects at risk for COPD. Nonetheless, the importance of the public health message, to highlight that the presence of cough and sputum in the population is abnormal, remained unchanged.

The GOLD 2011 Report, published in 2013 [12] (Figure 4), represented a substantial evolution to highlight for the first time that the aims of COPD treatment had to be mainly focused on two main patient-reported outcomes, symptoms and exacerbations. The key issue here was to recommend a multi-dimensional approach, apart from the measurement of FEV_1. The move from the prior FEV_1 assessment of 2001-06 Revisions alone to this new holistic, multi-dimensional approach, underlining symptoms and history of exacerbations together with spirometry represented a major change of paradigm, commonly known as the *GOLD ABCD* classification. When reading the previous versions of GOLD publications, it is clear that symptoms did matter. However, the notion of the previous documents was that the level of FEV_1 was crucial for assessing lung function severity and treatment. When the illustrative “COPD ladder” based on the GOLD stages was developed in the 2006 Revision, there was little

evidence to support this and an assessment scheme will only rarely be evidence based as few studies so far have tested different diagnostic criteria and/or assessment modalities. This revised document recommended assessment of symptoms, lung function, risk of exacerbations and comorbidities. A systematic assessment of COPD is necessary to ensure sufficient quality in the management of COPD. Regarding symptoms, GOLD suggests the modified Medical Research Council (mMRC) or COPD Assessment Test (CAT) scores but there are no reasons to use other symptom questionnaires, such as the Clinical COPD Questionnaire (CCQ) [12]. The fundamental issue here is to consider whether the patient has only mild symptoms or feels highly symptomatic. Subsequent GOLD updates may include other scales and the recommendation can be altered based on regional or national guidelines if other systems to assess symptoms are better suited locally. For risk of exacerbations, a history of two or more exacerbations per year indicates a high likelihood of future exacerbations, a cut-off scientifically supported [19]. Because of the impact of an exacerbation leading to hospital admission and mortality [20], one severe exacerbation requiring hospitalization will also indicate high risk. It was strongly recommended, first, to assess symptoms, and next, to assess risk of exacerbations. As for the management, the most crucial recommended non-pharmacologic treatments relate to physical training and physical activity, vital facets that cannot be overlooked at all. The recommendations for pharmacologic treatment are mainly related to choice of initial therapy. Compared to now, there was a clear lack of RCTs informing on treatment choices in case of lack of efficacy on first choice treatment. According to the GOLD scheme, "*First choice*" therapy is to be seen as initial therapy, whereas "s*econd choice*" treatments can be considered in patients not sufficiently well managed on initial therapy. It should also be recaled that evidence based recommendations are often based on group comparisons from RCTs and that in

the clinical real world, a significant proportion of patients will often do well on a treatment that may be slightly less efficacious in a large trial.

The GOLD 2017 Report refined the 2011 Report [14] (Figure 5). The most important refinement herein is that the two vertical axes (for airflow limitation, left-side, and for risk of exacerbations, right-side) of the GOLD 2011 Report seem to differ in their predictive power regarding the risk of exacerbations. The exacerbation history seems to be more relevant than the level of airflow limitation for the individual patient's risk to develop an exacerbation. This reasoning is crucial and this is why the spirometric evaluation is separated from the assessment of symptoms and the exacerbation history, while the pharmacologic treatment is now based only on the latter two components as illustrated in more detail in Figure 4. However, spirometry still remains highly relevant, not only for disease diagnosis but also for follow-up, particularly to take decisions regarding non-pharmacologic therapeutic issues and to identify rapid decliners. In order to tailor the medication to the individual patient's needs, algorithms are consequently mandatory and were developed (Figure 4) [14].

Final Remarks

The story and working process of GOLD during these last 20 years represent a firm commitment to be an actual blender of the evolving changes in the COPD world and, above all, a think tank continuously proposes inspiring concepts [21]. Indeed, GOLD has made a great contribution to capture the global COPD landscape and its very significant changes experienced over the last two decades. Irrespective of the own limitations of any global ambitious project, we have to agree that GOLD has the value of "putting

COPD globally in the 20th century world of the medical community" after many decades.

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FIGURES

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Figure 1

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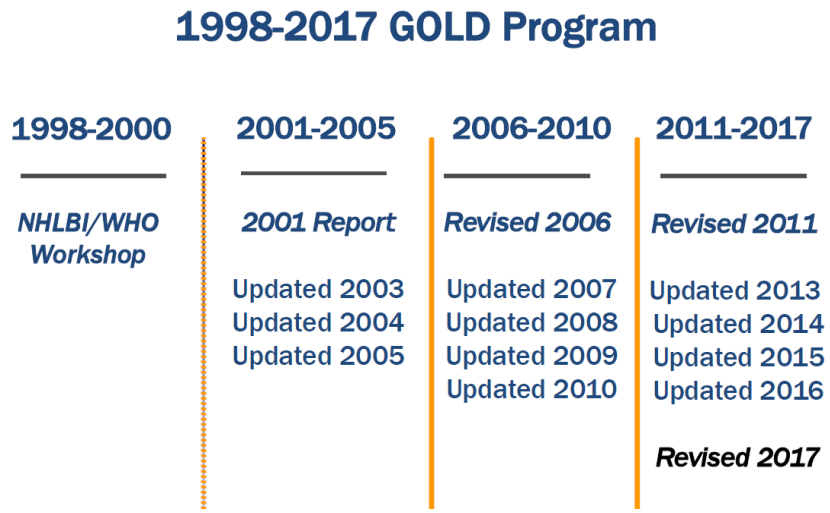

1998-2017 GOLD Program
1998-2000
NHLBI/WHO Workshop
2001-2005
2001 Report
Updated 2003
Updated 2004
Updated 2005
2006-2010
Revised 2006
Updated 2007
Updated 2008
Updated 2009
Updated 2010
2011-2017
Revised 2011
Updated 2013
Updated 2014
Updated 2015
Updated 2016
Revised 2017

Figure 3

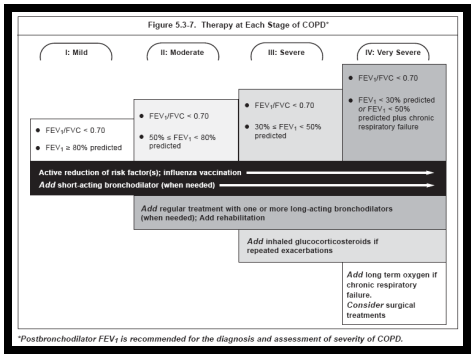
GOLD 2001

Figure 5-3-8. Therapy at Each Stage of COPD

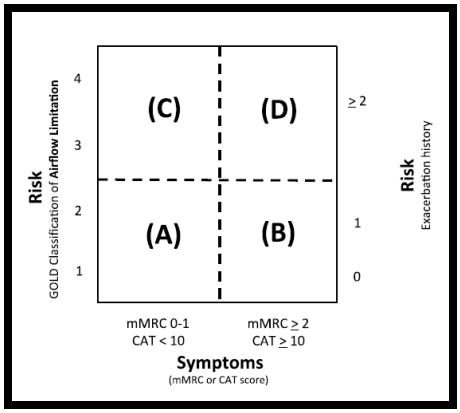
Patients must be taught how and when to use their treatments and treatments being prescribed for other conditions should be reviewed. Beta-blocking agents (including eye drop formulations) should be avoided.

Stage	Characteristics	Recommended treatment	
ALL		• Avoidance of risk factor(s) • Influenza vaccination	
0: At Risk	• Chronic symptoms (cough, sputum) • Exposure to risk factor(s) • Normal spirometry		
I: Mild COPD	• $FEV_1/FVC < 70\%$ • $FEV_1 \geq 80\%$ predicted • With or without symptoms	• Short-acting bronchodilator when needed	
II: Moderate COPD	**IIA:** • $FEV_1/FVC < 70\%$ • $50\% \leq FEV_1 < 80\%$ predicted • With or without symptoms	• Regular treatment with one or more bronchodilators • Rehabilitation	• Inhaled glucocorticosteroids if significant symptoms and lung function response
	IIB: • $FEV_1/FVC < 70\%$ • $30\% \leq FEV_1 < 50\%$ predicted • With or without symptoms	• Regular treatment with one or more bronchodilators • Rehabilitation	• Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations
III: Severe COPD	• $FEV_1/FVC < 70\%$ • $FEV_1 < 30\%$ predicted or presence of respiratory failure or right heart failure	• Regular treatment with one or more bronchodilators • Inhaled glucorticosteroids if significant symptoms and lung function response or if repeated exacerbations • Treatment of complications • Rehabilitation • Long-term oxygen therapy if respiratory failure • Consider surgical treatments	

GOLD 2006



GOLD 2011



GOLD 2017

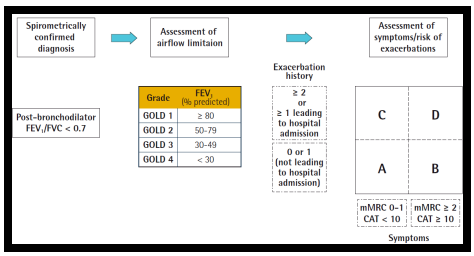
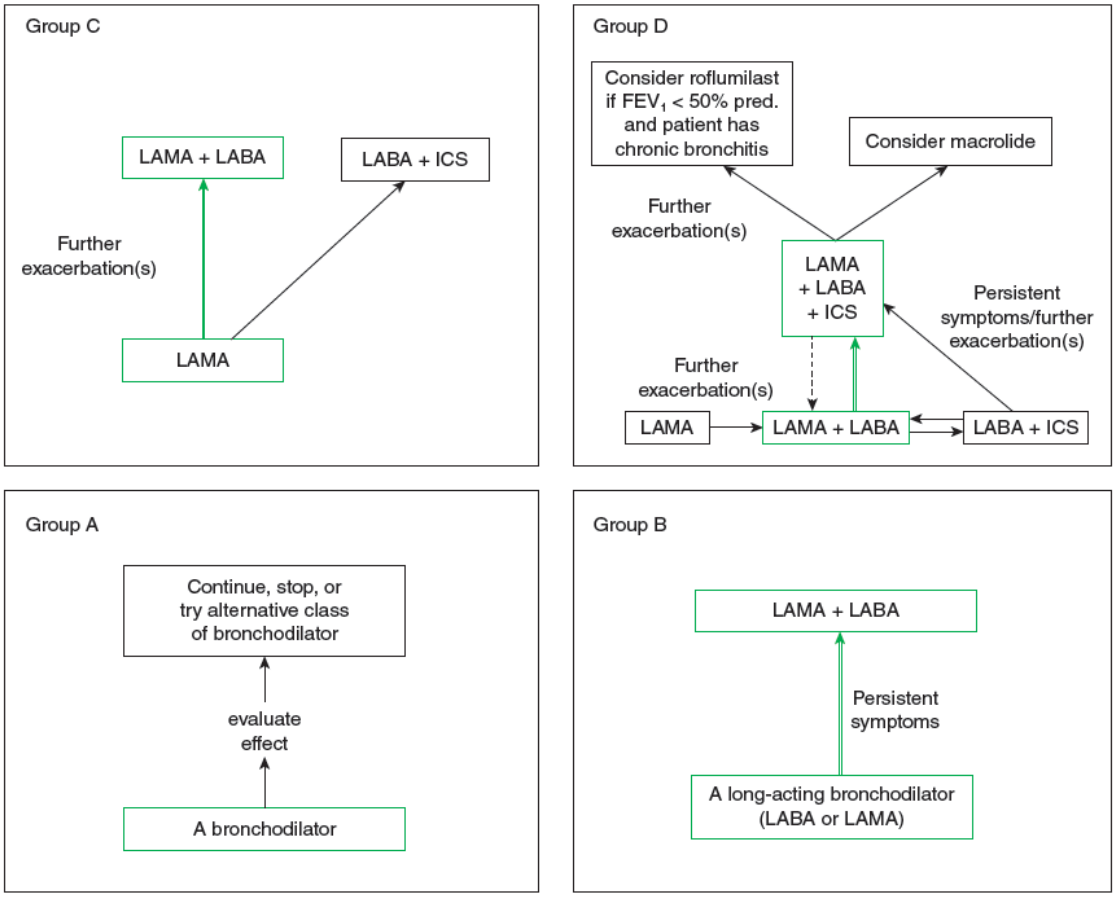


Figure 4



Preferred treatment = ⟹

In patients with a major discrepancy between the perceived level of symptons and severity of airflow limitation, further evaluation is warranted.

Figure 5

Legends

Figure 1. GOLD`s wall of fame. Claude Lenfant, Executive Director (2005-15), Suzanne S Hurd, Scientific Director (2000-15), and Romain Pauwels (2000-05) created and implemented the basis of the scientific and organization networks of GOLD.

Figure 2. Panel of the April 1998 Workshop of the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: NHLBI/WHO Workshop National Heart, Lung, and Blood Institute (NHLBI) (Director, Claude Lenfant) and World Health Organization (WHO) (Director, Nikolai Khaltaev). This entity created and developed the foundational body of GOLD (reproduced with permission from GOLD).

Figure 3. Historical scheme of the GOLD program highlighting the most relevant documents published (2000-17).

Figure 4. COPD assessment and classification as proposed by GOLD 2001, 2006, 2011 and 2017 Reports (from top to bottom). For further explanations, see text. Abbreviations: GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council; CAT: COPD Assessment Test (reproduced with permission from the publishers).

Figure 5. Pharmacologic treatment algorithms recommended for the four GOLD grouprs (A, B, C, and D) in the GOLD 2017 Report. Green boxes and arrows indicate preferred treatment pathways. FEV_1: forced expiratory volume in one second. ICS: inhaled corticosteroid; LABA: long-acting β-agonist; LAMA: long-acting muscarinic antagonist (reproduced with permission from GOLD).