

# Assessment of patients with chronic obstructive pulmonary disease (COPD) in GOLD 2011/2013: More grey zones or a step towards better management?

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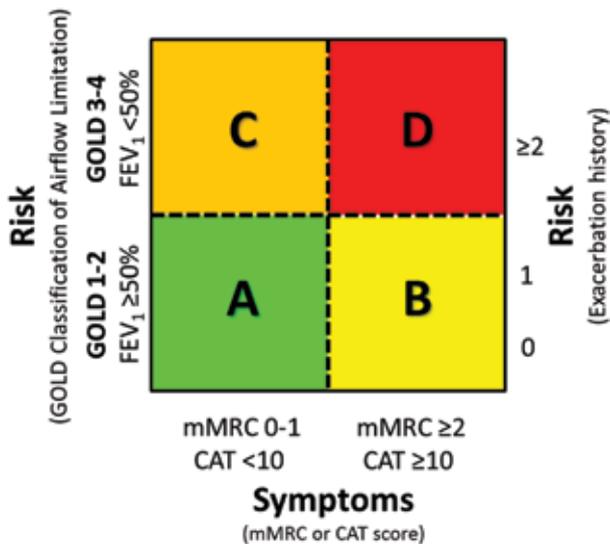
The Global Initiative for Chronic Obstructive Lung Disease (GOLD) was initiated in 1998 and provided the first recommendations for the management of chronic obstructive pulmonary disease (COPD) in the “Global Strategy for Diagnosis, Management and Prevention of COPD” report that was issued in 2001. Since then two complete revisions have been made, in 2006 (published in 2007)<sup>1</sup> and in 2011<sup>2</sup>, with continuous attempts to provide a yearly update of the GOLD report, the most recent being that in early 2013<sup>3</sup>. The recommendations of the GOLD report are based on a well-established literature review followed by thorough evaluation by the GOLD committee members.

The major change in the 2011 GOLD report was an attempt to provide a new classification of patients with COPD into 4 categories, groups A to D, based on a multi-component system that includes evaluation of the patient’s symptoms and the future risk of exacerbation<sup>2</sup>. Patients were classified as less (groups A or C) or more symptomatic (groups B or D) based on the modified Medical Research Council (mMRC) scale or the COPD Assessment Test (CAT) (Figure 1). In the 2013 revision, the Clinical COPD Questionnaire (CCQ) was also included<sup>3</sup>. Patients were additionally classified according to their risk for future events (exacerbation, hospitalization or death) into low risk (groups A and B) and high risk (groups C and D), according to the severity of airflow obstruction and the history of exacerbations ( $\geq 2$  in the previous year). In the 2013 revision, a history of one hospitalization in the previous year is a further criterion that classifies patients into the high-risk group, as the GOLD Committee recognized that one severe exacerbation requiring hospital admission was sufficient to indicate a high risk of subsequent exacerbations<sup>3</sup>. Details of this classification system can be found in a supplementary issue of *Pneumon*<sup>4</sup>.

This new classification is now proposed as a more comprehensive way of evaluating the individual patient with COPD beyond the single-dimensional spirometric approach. The inclusion of evaluation of symptoms incorporates the long-standing clinical practice of asking our patients questions about their dyspnoea, using (deliberately or automatically) questions included in

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**FIGURE 1.** Classification of patients into groups A, B, C and D, according to their symptoms and the presence of high risk according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013. When assessing risk, choose the highest risk according to GOLD grade or exacerbation history. (One or more hospitalizations for COPD exacerbations should be considered high risk)<sup>3</sup>. COPD = chronic obstructive pulmonary disease, mMRC = modified Medical Research Council scale, CAT = COPD Assessment Test.

the mMRC dyspnoea scale. The proposed questionnaires (CAT or CCQ) are more comprehensive but rather time-demanding and have not been widely incorporated in everyday clinical practice, despite their increasing use in research. What is more welcome in the GOLD 2011/2013 report is that it represents the first attempt at a phenotypic approach to the management of patients with COPD, by including the “frequent exacerbator” phenotype, as acute exacerbations are the major risk factor for unfavourable outcomes in the natural history of COPD<sup>5</sup>. Patients with frequent exacerbations (defined arbitrarily as 2 or more in the previous year in the ECLIPSE cohort<sup>6</sup>) represent an independent susceptibility phenotype that remains quite stable over 3-year follow-up<sup>6</sup>. How easy is it for the practising clinician to identify these “frequent exacerbators”? A detailed history of events treated with systemic corticosteroids and/or antibiotics in the previous year, as recollected by the patients themselves, is probably sufficient and constitutes the best predictor of future exacerbations<sup>6</sup>. Although this new GOLD approach appeared to be reasonable, the evidence behind the new classification system was somewhat scarce at the

time of its initial presentation, and it has been widely commented upon<sup>6-8</sup> and even criticized by COPD experts<sup>9</sup>.

In the past year, a few publications have attempted to evaluate the GOLD 2011 proposal in well-characterized cohorts of patients<sup>10-15</sup>. In the majority of the relevant studies, the classification of patients into the 4 groups was uneven and quite different from the distribution with the previous system, with groups A and D being the largest and groups B and C the smallest. In the well-defined prospective ECLIPSE cohort, the classification was 24% in group A, 14% in group B, 23% in group C and 40% in group D (compared with 44% in stage II, 42% in stage III and 14% in stage IV)<sup>10</sup>. During the 3-year follow-up, most of the patients in groups A and D remained in their original classification, whereas the patients in groups B and C showed greater temporal variability, with group B patients remaining in the same category, improving or deteriorating in similar proportions, while the majority of group C patients either remained stable or deteriorated<sup>10</sup>. In another prospective study, that of the COPDgene cohort, Han and colleagues documented similar findings, but with the group B being the smallest; that study, however, showed significant differences between the classification of symptoms according to the mMRC dyspnoea scale and the Saint George’s Respiratory Questionnaire (SGRQ) (as a surrogate for the CAT score, based on the significant agreement between the two tools)<sup>11</sup>. This important finding underlines the need for better standardization of the cut-off points of the various different symptom assessment tools, so that they can be used interchangeably, as the classification is currently rather arbitrary in the GOLD 2011 paper.

The most important message derived from all these cohort studies is the wide discrepancy between the ability to predict survival of patients with COPD of the 4 groups, A-D, and that of the GOLD 2007 classification that was based only on spirometry. In a cumulative analysis of 11 cohorts in Spain followed for up to 10 years, Soriano and colleagues showed that the 2011 classification did not differ from the old classification in its prognostic validity to predict time to death<sup>15</sup>; an important drawback of this study, however, was the significant heterogeneity of the 11 original cohorts. Similar results were derived in the cohort of the GenKOLS study in Norway<sup>12</sup>. In contrast, in another cohort from the HUNT study in Norway, Leivseth and colleagues showed that the spirometric classification of GOLD 2007 actually predicted mortality better than the GOLD 2011; in the latter mortality was generally similar in groups A and B, and in groups C and D<sup>14</sup>. In an analysis of

the ECLIPSE cohort, both classifications were similar in the prediction of all-cause mortality, but in the comparison among individual groups, mortality was lowest in group A and highest in group D, but similar (and intermediate) in patients from groups B and C<sup>10</sup>. Finally, in a study of a cohort generated from two population studies in Copenhagen, patients in group B had significantly worse survival than the “higher-risk” patients in group C, a finding that was attributed to higher mortality from cardiovascular disease and cancer in group B<sup>13</sup>. This study suggests that the presence of comorbidities in group B patients, who are characterized by significant symptoms in the presence of relatively well preserved lung function, needs special attention in the management of these patients.

Regarding the hot issue of COPD exacerbations and hospitalizations, these have been reported in the currently available studies to be relatively increased in the two high-risk groups, C and D<sup>10,11,13</sup>. An interesting observation, however, lies in the differences in exacerbation rates according to the reasons for classification in these two groups. In the Copenhagen study, Lange and colleagues classified patients according to the presence of low FEV<sub>1</sub> (C1 or D1),  $\geq 2$  exacerbations in the previous year (C2 or D2), or both (C3 or D3). Using this classification, these authors showed that: 1) the majority of patients had been classified according to the presence of severe airflow obstruction (C1 75% and D1 79%), and 2) the patients that had been classified based on the “frequent exacerbations” criterion (C2/C3 and D2/D3) were those who presented more exacerbations during follow-up<sup>13</sup>. In a similar analysis, Han and colleagues provided further support of these results in the COPDgene cohort, showing that patients with a history of exacerbations (with or without FEV<sub>1</sub> <50%) were more likely to develop exacerbations during longitudinal follow-up, compared with those characterized only by severe airflow obstruction, especially those in group D<sup>11</sup>. These findings further strengthen the importance of a history of frequent exacerbations as a strong predictor of future events.

The most important disadvantage of all the studies discussed here is the fact that they are based on retrospective or – at best – post-hoc analysis of previously collected data, and this is the most plausible explanation of their discrepancies. In spite of their drawbacks, however, these studies have provided important insight into the new classification system proposed by the 2011/2013 GOLD document and they do support the need for multi-dimensional assessment of each individual patient with COPD. The messages derived across all these populations

are: 1) the importance of symptoms, and especially dyspnoea, with special attention to be given to the symptomatic patients with well preserved lung function in group B, 2) the importance of the history of exacerbations, which constitute the single most important predictor of future events, and 3) the overriding importance of spirometric classification that remains the cornerstone of evaluation of patients with COPD. One other issue that has been raised by these studies is something that the GOLD 2011/2013 reports simply whisper: comorbidities. The presence of comorbidities, the most important of which is cardiovascular disease, has emerged as a significant predictor of future risk for patients with COPD<sup>16</sup> and this is the new dimension that the pulmonary community should start considering routinely in their management. The new GOLD reports are definitely a step in the right direction, but the classification needs to be refined through well-designed and carefully conducted prospective clinical trials. Until the findings of such trials are available, we should treat the current GOLD 2011/2013 document simply as a reminder of what we, as clinicians, should have been doing, based on the best currently available evidence.

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