



A new alphabet for COPD care: where “E” stands for España

To the Editor:

We read with interest the editorial by KERWIN [1] on the management of chronic obstructive pulmonary disease (COPD). This editorial follows the publication of the AFFIRM trial showing the superior bronchodilating effects of a long-acting muscarinic antagonist (LAMA)/long-acting β -agonist (LABA) combination over an inhaled corticosteroid (ICS)/LABA combination in a head-to-head trial, although symptom-based outcomes were not different [2]. These findings replicate those of the FLAME trial showing non-inferiority between a LAMA/LABA over an ICS/LABA combination, although reductions in exacerbations were greater in the former [3]. We would like to endorse the view of KERWIN [1] and VOGELMEIER *et al.* [4] that it is a good time to “refine the paradigmatic GOLD classification”.

First, we like the addition of the E category in this classification system and suggest it might stand for “España”, acknowledging that the Spanish were among the first to recognise that asthma–COPD overlap syndrome (ACOS) was of sufficient importance to require special consideration in their COPD management guidelines [5]. We also note that ACOS, defined in part by atopy, is characterised by IgE-mediated (“E”) diseases such as allergic rhinitis, atopic dermatitis, skin test positivity for common aero-allergens and elevated serum IgE titres [4]. ACOS has now attracted a lot of attention as a sub-phenotype of COPD, representing between 15–20% of patients [1, 6]. However, while we agree that the evidence suggests that eosinophil-related COPD and “frequent exacerbators” are responsive to ICS [1], we do not think they should be grouped with ACOS in category “E” [1]. This is primarily because patients with ACOS are almost always excluded from COPD clinical trials. This is particularly relevant when comparing outcomes between ICS/LABA and LAMA/LABA combinations in head-to-head trials (*e.g.* FLAME and AFFIRM [2, 3]) or substitution trials (*e.g.* WISDOM [7]). We suggest that the results of these “COPD” trials cannot yet be generalised to ACOS patients (discussed further below). Given this caveat, we propose an alternative schema to the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) A-to-D strategy (<http://goldcopd.org/>), where the “E” (España/IgE) category represents patients with ACOS exclusively (figure 1). We outline below why we believe this alternate schema maintains much of the utility of GOLD 2011 in helping rationalise inhaler therapy in COPD [4–6, 8].

One of the key reasons for proposing the GOLD A-to-D categories in 2011 was to encourage doctors to tailor their choice of inhaler therapy according to the patient’s symptoms and exacerbation history, rather than to just the severity of their airflow obstruction [4, 8]. This remains a key concept in the overall principles governing the management of COPD. In our A-to-E schema (figure 1), we believe these principles are better preserved than in the A-to-E schema proposed by Kerwin. A second reason we prefer to build on the existing GOLD A-to-D category schema is the principle that the majority of COPD patients will transition between two or more categories. This allows a “step-up” approach (escalation) where inhaler use in COPD, much like in asthma, progresses from short-acting reliever medications to combinations of long-acting preventer/reliever medications [4, 8]. This also allows a “step-down” treatment approach (de-escalation) for patients who are stable or not tolerating an existing therapy [4, 8]. This is particularly relevant to the usage of ICS in COPD, where the risk of numerous complications (*e.g.* pneumonia, cataracts or osteoporosis) must be weighed against the perceived benefits (reducing exacerbations, preventing hospitalisation and preserving lung function). While many of these complications might be avoided by using low dose ICS, complete ICS withdrawal may be clinically indicated for some patients. In this regard, while the studies showing non-inferiority between LAMA/LABA combinations compared to ICS/LABA combinations are reassuring [1], the results do not apply to patients with ACOS (see above). A third reason we favour our suggested schema is that patients with COPD or ACOS, characterised by irreversible or

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An alternative schema to the 2011 GOLD A-to-D strategy, where the “E” category represents patients with ACOS only <http://ow.ly/BGiN3069GKD>

Cite this article as: Young RP, Hopkins RJ. A new alphabet for COPD care: where “E” stands for España. *Eur Respir J* 2017; 49: 1601970 [<https://doi.org/10.1183/13993003.01970-2016>].

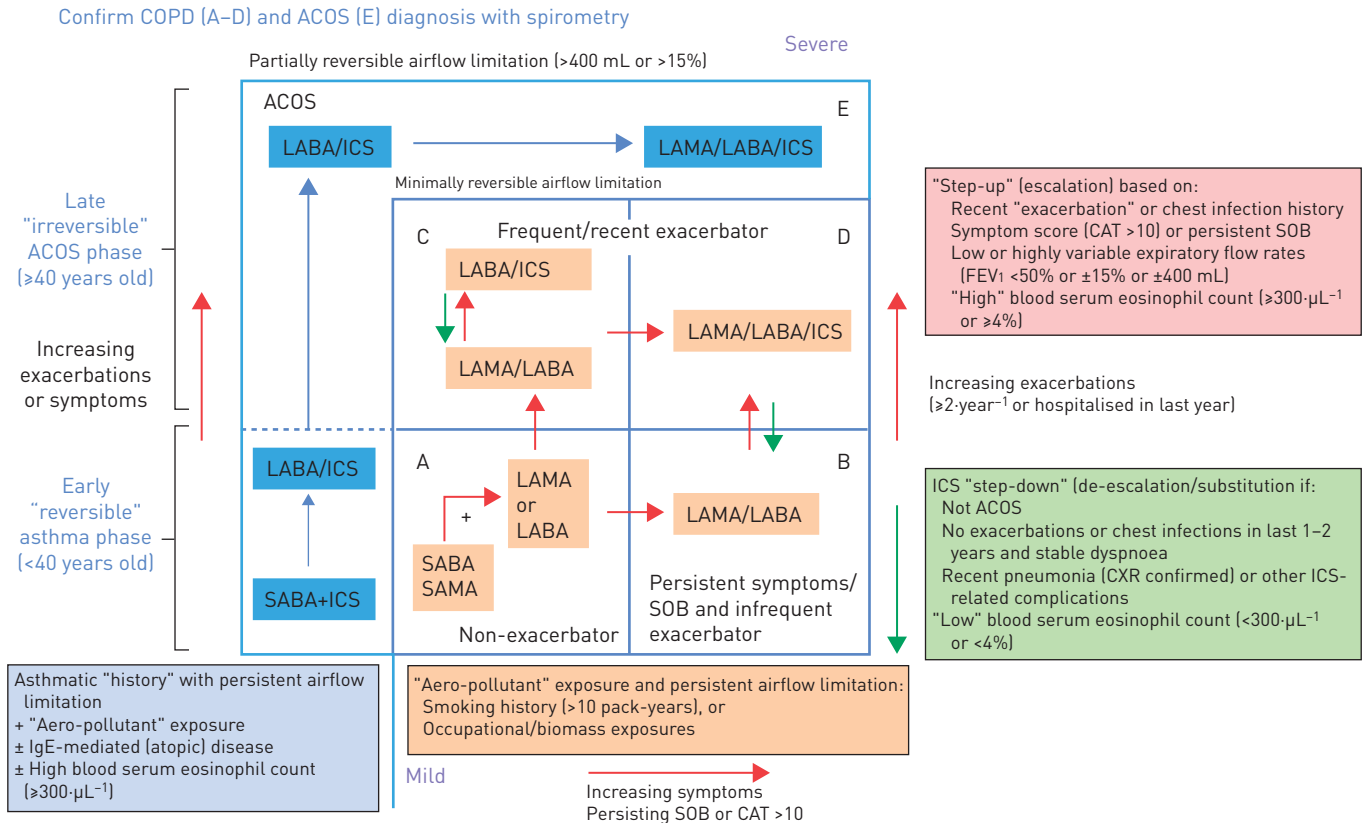


FIGURE 1 Alternate schema to the 2011 GOLD A-to-D chronic obstructive pulmonary disease (COPD) management strategy. ACOS: asthma–COPD overlap syndrome (defined in [6]); CAT: COPD-assessment test; ICS: inhaled corticosteroids; LABA: long-acting β -agonist; LAMA: long-acting muscarinic antagonist; SABA: short-acting β -agonist; SAMA: short-acting muscarinic antagonist; SOB: shortness of breath; FEV₁: forced expiratory volume in 1 s; CXR: chest radiograph.

partially reversible airflow limitation on spirometry [1, 4], are also sub-phenotyped according to their past history of smoking, occupational exposure, asthma and atopic disease (figure 1). In this setting, we have suggested that frequent/recent exacerbators with eosinophil-related COPD, in the absence of any asthma or atopy history, would be better placed in category C where an ICS/LABA combination might be chosen over a LAMA/LABA combination for the reasons outlined by KERWIN [1]. While we accept that there will continue to be debate about just which cut-off points best represent steroid-responsive COPD [9, 10], and for whom continuation of ICS may be most beneficial (or least deleterious), we suggest that serum eosinophil levels of more than 2–4% (or 150–300 cells- μL^{-1}) are good starting points [10]. No doubt future debate will focus on this issue.

In summary, we propose a modified version of the 2011 GOLD A-to-D quadrants, in which adding an "E" category to the existing schema offers a viable alternative to that suggested by KERWIN [1]. We believe that our alternate schema maintains the intended principles of COPD management proposed by the 2011 GOLD recommendations.

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Received: Oct 06 2016 | Accepted: Oct 07 2016

Conflict of interest: None declared.

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*From the author:*

In their correspondence, R.P. Young and R.J. Hopkins helpfully identify the Spanish guidelines [1] for chronic obstructive pulmonary disease (COPD) which, along with a later publication [2], have helped specify key subgroups of COPD (marked by high eosinophil count, personal history of asthma or atopy, or positive IgE or skin tests) who potentially have an asthma–COPD overlap syndrome (ACOS) component benefiting from inhaled corticosteroid (ICS)/long-acting β -agonist (LABA) combinations. Not so helpful in profiling ACOS patients are forced expiratory volume in 1 s reversibility criteria, since up to 50% of all COPD patients may reverse over 12% and 200 mL after bronchodilator use [3–5].

There is a need to better define and prospectively study ACOS. For now, *post hoc* analyses of completed COPD studies have begun to confirm that ICS therapies can benefit COPD subgroups with high eosinophil counts and exacerbation risks [6]. Other subgroups with strong potential to benefit from ICS include COPD patients with a history of atopic disease, onset before age 40, and patients with positive IgE or skin test history.

Guidelines need to be transparent and provide clear therapeutic direction in the fashion of a road traffic signal: green, yellow, or red. The current Global Initiative for Chronic Obstructive Lung Disease (GOLD) A, B, C and D classes do not clearly identify “ICS-needy” patients. Instead, all categories of GOLD patients utilise ICS/LABA combinations and this can be like looking at a traffic light through fog. While Young and Hopkins appropriately identify several ACOS risk factors, and stress escalation of therapies when needed, they still leave a muddle where GOLD A, B, C and D groups all contain “ICS-needy” patients.

The proposed “E” group (including three subgroups with frequent exacerbations, high eosinophil counts, or IgE–asthma components) would help to clear the fog and direct clinicians to utilise ICS/LABA and ICS/LABA + long-acting muscarinic antagonist (LAMA) combinations for this new “E” group where patients are most likely to benefit. Remaining GOLD A, B, C and D patients may thrive with LAMA/LABA bronchodilator combinations. In the future, more specific pathophysiologic ACOS biomarkers (such as IL4, IL5, IL13, IL33, TSLP, periostin and others) may help to better identify ACOS and direct therapies to specific phenotypic subgroups in the totality of patients with COPD.

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A revised GOLD guide should identify patients likely to benefit from inhaled corticosteroids/long-acting β -agonists <http://ow.ly/mXxM306bDeN>

Cite this article as: Kerwin E. A new alphabet for COPD care: where “E” stands for España. *Eur Respir J* 2017; 49: 1602067 [https://doi.org/10.1183/13993003.02067-2016].

Received: Oct 21 2016 | Accepted: Oct 24 2016

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

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