ALGORITHM FOR THE WITHDRAWAL OF INHALED CORTICOSTEROIDS IN COPD

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The use of inhaled corticosteroids (ICS) along with long-acting β2-agonists (LABA) has been common for COPD (Chronic Obstructive Pulmonary Disease) patients for years, based on studies which have shown a decrease in exacerbations compared to bronchodilators or ICS separately[1]. This trend has continued over time, in spite of new evidence referenced in guides which has limited the indications for ICS in the treatment of COPD[2, 3]. Several studies have shown an overprescription of ICS for COPD patients if we look at the current indications included in the guides[4, 5],in addition to showingthe continued use of ICS is associated with several complications, notably pneumonia[1, 6].

This algorithm (Figure 1) integrates a series of recommendations to select those patients who do not have an indication for ICS, in addition to providing guidelines for follow-up once they have been withdrawn.

1. Starting criteria:

- The first, presence of criteria for the ACO (asthma COPD overlap) phenotype, is based on the better response to ICS from patients with criteria for ACO, certified by the GOLD (Global Obstructive Lung Disease) guide and GesEPOC (Guía Española de la EPOC)[2, 3], although the criteria we have chosen to define ACO are those from the document of recommendations for the diagnosis and treatment of COPD in Andalusia[7](Table 1).
- EFor the second criterion we have included wheezing in the stable phase, which is a clinical criterion based on experts' experience. We believe that patients who present nearly constant or frequent wheezing, especially predominant at night and not just during exacerbations, are not candidates for ICS withdrawal.

The number of eosinophils has also been included in this section, based on several publications which have shown a decrease in exacerbations in patients treated with ICS when there is an elevated eosinophil count in peripheral blood[8, 9]. In our case, we considered a value of ≥300 eosinophils/μL in peripheral blood, as withdrawal of ICS in these cases has been shown to be accompanied by an increase in the number of exacerbations[10].

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- The third criterion, not having had severe exacerbations or having fewer than 2 moderate exacerbations in the previous year, is also based on the criteria from current guides which classify these patients as being at low risk of exacerbations[2, 3].

If the patient meets the initial assessment criteria, ICS can be stopped and substituted by double bronchodilation (DBD).

If the initial criteria are not met, if it is due to having ACO criteria and/or presenting frequent wheezing in the stable phase and/or having a peripheral blood eosinophil count of ≥300 cells/µL, ICS will not be withdrawn and the initial dosage will be maintained.

If criteria are not met because the patient has had a severe or more than 1 moderate exacerbation, if he or she is receiving a high dosage of ICS an attempt can be made to move down to a medium dosage (recommended dosages shown in Table 2) and also maintain DBD, especially if the patient has a history of pneumonia.In these cases, alternative treatments with ICS can be considered, such as those shown in Table 3.

Table 1: ACO *(Asthma COPD Overlap)* criteria. Taken from the document of recommendations for the diagnosis and treatment of Chronic Pulmonary Obstructive Disease in Andalusia[7]

Main criteria (mandatory)	FEV_1* reversibility ≥12% (and greater than 200 ml in absolute values)
and at least 2 of the following criteria:	1. Personal or family history of asthma or atopy 2. Frequent wheezing, especially predominant at night and not only during exacerbations 3. Elevated IgE 4. Peripheral blood eosinophil count of ≥300 cells/µL without another justifying cause

*FEV_1: maximum volume exhaled in the first second

Table 2. Inhaled corticosteroid dosage*

Drug	Low dosage (mg/day)	Medium dosage (mg/day)	High dosage (mg/day)
Extra fine beclomethasone	100 – 200	201 - 400	>400
Fluticasone propionate	100 – 250	251 - 500	501 - 1,000
Budesonide	200 – 400	401 - 800	801 - 1,600

- Fluticasone furoate: the only available dosage for EPOC is 92 mg/day.

*Only ICS combined with LABAs that are approved in the COPD fact sheet are shown.

Table 3: Other treatment alternatives

Drug	Indication
Roflumilast	For patients with the chronic bronchitis phenotype and FEV_1* <50%.
Theophylline	For patients with the emphysema phenotype
Azithromycin	Severe and very severe COPD with frequent exacerbations that require several antibiotic treatments, despite an optimum treatment.

*FEV_1: maximum volume exhaled in the first second.

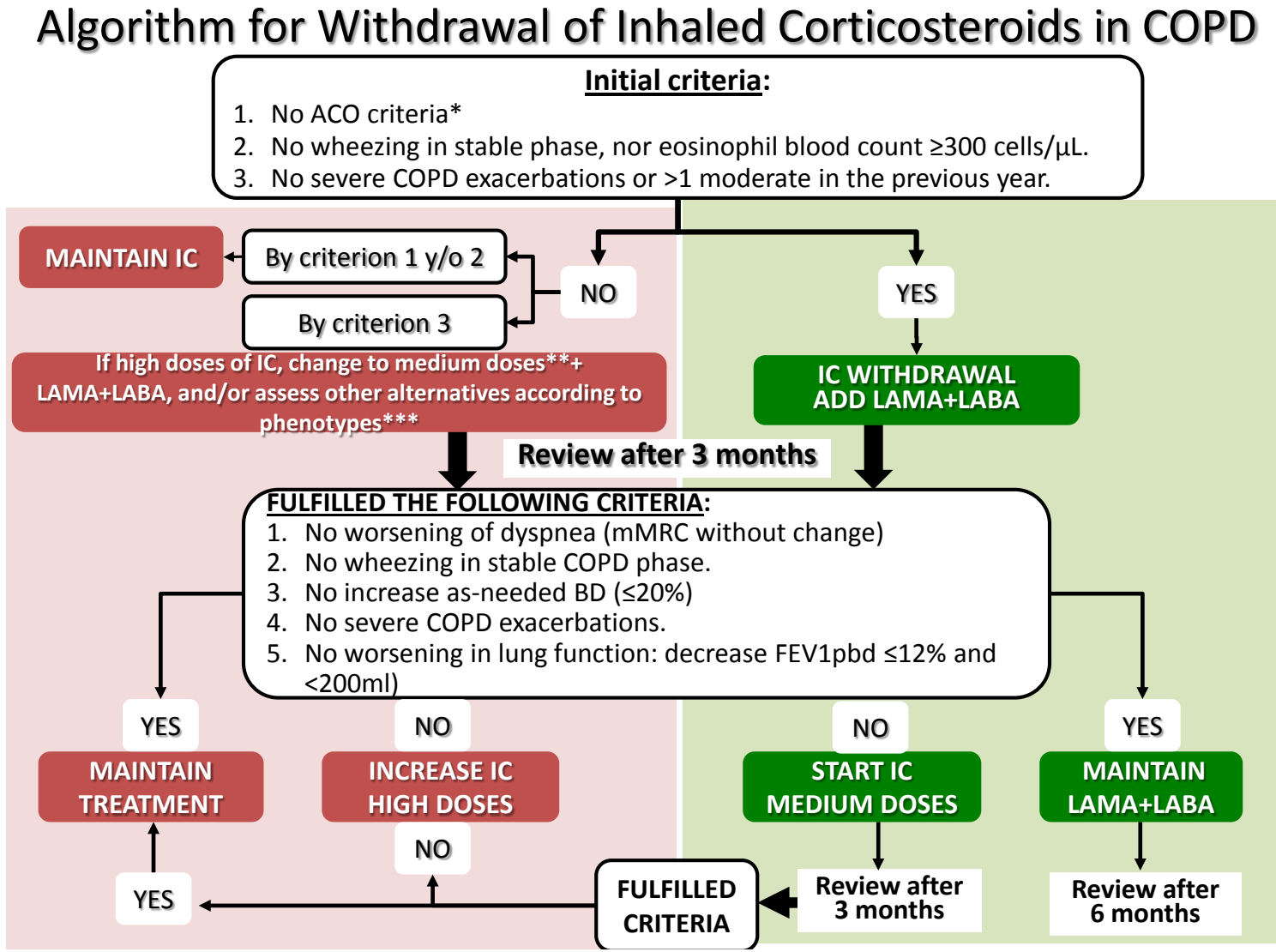

Figure 1. Algorithm for the withdrawal of inhaled corticosteroids (ICS) in COPD.
*ACO:asthma COPD overlap. See Table 1. **: See Table 2. ***: See Table 3. LAMA: long-acting muscarinic antagonist. LABA: long-acting β2-agonist.
FEV_1: maximum volume exhaled in the first second.mMRC: Modified Medical Research Council Dyspnea Scale.

2. Progress criteria.

In any of the cases, both withdrawing and reducing the ICS dosage, the patient will be examined after 3 months and, if they meet the progress criteria, treatment will be maintained.The following are the criteria we have selected to determine whether progress has been favorable.

- No worsening from baseline dyspnea: if the patient shows worsening of the baseline dyspnea after three months according to the mMRC (Modified Medical Research Council) scale, which is not justified by other reasons, ICS will have to be reintroduced, especially when the dyspnea, and lung function, is a parameter which improves with DBD compared to LABA+ICS treatment.
- Appearance of frequent wheezing in the stable phase: this will be a criterion we feel is a clinical indication of bronchospasm and very likely indicates the existence of bronchial hyperreactivity, thus ICS would need to be reintroduced.This is a clinical criterion based on experts' opinions.
- Increase in rescue medication: although this parameter is difficult to quantify, a significant increase in rescue medication will force us to consider reintroducing ICS.The quantification of the increase in rescue medication is based on the results of the FLAME study[11], which showed a 25% reduction in the use of rescue medication (average reduction of 1 daily inhalation), using patients with an average of 4 inhalations per day as the baseline.We believe that changing treatment to DBD should reduce the use of rescue medication, but if there is a 20% increase in its use, we believe progress is not favorable.However, this parameter is difficult to quantify. As a result, this criterion must be evaluated with caution.
- No severe acute exacerbations of COPD (AECOPDs): although follow-up is only 3 months, if the patient has a severe AECOPD, especially if it is non-infectious, we must consider reintroducing ICS.If there is only one case of moderate AECOPD, reintroducing ICS will not be necessary.The FLAME study[11] has shown that DBD is better than the LABA+ICS combination in patients with a single moderate AECOPD. If there were more than one moderate AECOPD, we would need to consider reintroducing ICS at a medium dosage, although 3 months is likely a short time for 2 moderate AECOPDs to occur.
- Drop in lung function: we have set a limit of 12% and always above 200 ml. If the patient's FEV_1 falls below this level after withdrawing the ICS, they would meet significant reversibility criteria, indicating they would likely benefit from ICS and that at the time of evaluation they were not influenced by bronchodilator treatment for some reason.

It is not common to see worsening in only one of these progress criteria, thus worsening in patient's progress after withdrawing ICS is usually accompanied by the worsening of more than one criterion, which reinforces introducing new ICS treatments.

Those patients for whom we have withdrawn ICS and who meet the progress criteria for stability will receive follow-up at 6 months, after which they will be reevaluated with the same criteria.

For patients who do not meet the progress criteria for stability, ICS at a medium dosage can be resumed, if they had been suspended, or higher dosages of ICS can be prescribed if the patient had been lowered to a medium dosage.

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