SUMMARY OF EVIDENCE

Appropriate use and withdrawal of inhaled corticosteroids in patients with COPD

Objective

The purpose of this summary of evidence for withdrawal of IC S is to:
1. Help identify patients who would benefit from ICS treatment vs those in whom it may not be appropriate, and
2. Provide guidance on how to withdraw ICS in COPD patients in whom it is not needed.

Introduction

• In COPD, bronchodilation is recommended as first line treatment for all patients classified as GOLD A or B. GOLD B patients on monotherapy should step up to LABA+LAMA if symptoms persist, and for patients with severe breathlessness, initial therapy with two bronchodilators may be considered. Initial therapy for patients in GOLD C is a LAMA, with the preferred step up to LAMA+LABA. In GOLD D, LABA+LAMA is the preferred first line treatment. In GOLD C and D, if exacerbations persist, ICS can be added (GOLD 2017).

• The use of ICS should be reserved for patients with concomitant asthma; if asthma is present, patients should be treated according to the GINA Strategy Report (ICS is indicated from Step 2, or as an “other controller option” at Step 1), plus a long-acting bronchodilator (either as part of the GINA-recommended regimen or added to treat COPD) [GINA; 2016; GINA-GOLD ACOS report 2013].

• Patients with a history of ≥2 exacerbations per year or ≥1 leading to hospital admission, who after LABA+LAMA therapy have further exacerbations (GOLD 2017).

• Despite years of recommendation that ICS use should be reserved for patients with predicted FEV1 <50% and repeated exacerbations [GOLD 2001], there is evidence of inappropriate use of ICS in COPD patients [Vestbo 2014; Price 2014; Burgel 2014; Corrado 2012; de Miguel-Díez 2011].

• Long-term ICS use is associated with a significant risk of pneumonia [Yawn 2013; Sussia 2013; Kew & Seniukovich 2014], and systemic effects [Price 2013].

• ICS use was associated with a dose-related increase in the risk of pneumonia, with adjusted hazard ratios versus no use of 1.38 (low-dose), 1.69 (medium-dose) and 2.57 (high-dose; all p<0.01) [Yawn 2013].

• Current use of ICS was associated with a 69% increase in the rate of serious pneumonia (RR 1.69; 95% CI 1.63, 1.75). The risk was sustained with long-term use [Sussia 2013].

• ICS use was associated with increased risk of serious adverse pneumonia events requiring hospital admission versus placebo (OR 1.78; 95% CI 1.50, 2.12) [Kew & Seniukovich 2014].

• The rate of pneumonia was significantly higher in patients receiving treatment with salmeterol/...
Part 1: How to identify if a patient would benefit from ICS

### History and biomarkers

For all patients currently treated with an ICS-containing regimen

1. **Check for asthma**
   - Consider asthma if patient has a documented history of asthma with or without atopy (we suggest that diagnoses made for people under 40 are more likely to be correct) [Sin 2016; Kaplan 2015]
   - Patient shows a large degree of airflow limitation reversibility (≥15% and ≥400 mL in post-bronchodilator FEV1) [Sin 2016]

   - A reported lack of efficacy of ICS, an elevated risk of adverse effects (including pneumonia) and evidence showing no significant harm from withdrawal supports the recommendation that ICS therapy can be stopped [GOLD 2017].

   - Recent studies have indicated that ICS discontinuation was associated with a 37% decrease in COPD exacerbations [Rossi 2014a].

   - The use of background long-acting bronchodilator medication may minimise any effect of ICS withdrawal [GOLD 2017].

   - In WISDOM, in high-risk patients randomly assigned to continued triple therapy or withdraw fluticasone in three steps over a 12-week period, ICS withdrawal met the prespecified non-inferiority criterion with respect to the first moderate or severe COPD exacerbation (HR 1.06; 95% CI 0.94 to 1.19) [Magnussen 2014].

   - In two post hoc analyses, data from the WISDOM trial were used to assess whether patients with COPD and diabetes mellitus would be more likely to have exacerbations if ICS treatment was withdrawn and if further stratification was possible when correlating eosinophil levels with exacerbation history.

   - After ICS withdrawal, the moderate or severe exacerbation rate was significantly higher versus the ICS-continuation group in patients with eosinophil counts ≥4% or ≥300 cells/µL [Watts 2016].

   - Withdrawal of ICS only increased exacerbation rates in patients with both raised eosinophil counts (≥400 cells/µL) and a history of frequent exacerbations (≥2) [Calverley 2016].

   - Recent studies have indicated that ICS can be withdrawn in both low- and high-risk patients, provided adequate bronchodilator therapy is in place [Rossi 2014a; Rossi 2014b; Magnussen 2014].

   - In INSTEAD, in low-risk patients, there was no significant difference between maintaining treatment with LABA/ICS combination salmeterol/fluticasone propionate and switching to LABA (indacaterol) in terms of breathlessness, health status, rescue medication use or COPD exacerbations [Rossi 2014a].

   - In OPTIMO, low-risk patients on ICS plus bronchodilator maintenance therapy experienced no deterioration of lung function symptoms, and exacerbation rate upon ICS withdrawal compared with patients continuing ICS treatment [Rossi 2014b].

   - In WISDOM, high-risk patients randomly assigned to continued triple therapy or withdraw fluticasone compared with placebo (19.6% versus 12.3% respectively; p=0.001) [Calverley 2007].

   - Pneumonia was reported in 8% and 4% of 1,499 patients treated with salmeterol/fluticasone and tiotropium, respectively

     - The hazard ratio for time to reported pneumonia was 1.94 (95% CI 1.19, 3.17; p=0.008) for salmeterol / fluticasone compared with tiotropium over 2 years [Wedzicha 2008].

   - A meta-analysis of 16 randomised controlled trials (17,513 participants) and 7 observational studies (69,000 participants) demonstrated that long-term exposure to fluticasone and budesonide is associated with a significant increase in the rate of fractures [Sikka 2011].

     - Over 3-years of treatment, each 500 µg increase in beclomethasone daily dose equivalents was associated with a 9% increased risk of fractures (95% CI 1.06 to 1.12; p<0.001) [Sikka 2011].

   - ICS use is associated with increases in the risk of diabetes onset and diabetes progression and is more pronounced at higher prescribed doses of ICS [Suissa 2010].

     - Patients with comorbid COPD and type 2 diabetes mellitus had significantly greater increases in HbA1c values when treated with ICS compared with those prescribed non-ICS therapies (higher HbA1c values are associated with a greater risk of the development of diabetes-related complications) [Price 2016].

   - Patients with comorbid COPD and atopy; (we suggest that diagnoses made for people under 40 are more likely to be correct) [Sin 2016; Kaplan 2015]
Part 1: How to identify if a patient would benefit from ICS (continued)

Consider maintaining ICS only if patient has:

1. Asthma
OR
2. High exacerbation risk AND high blood eosinophils
   - If necessary, continue ICS treatment in combination with appropriate long-acting bronchodilation (monitor for potential ICS-related adverse events)

Consider withdrawing ICS if patient has (see Part 2):

1. No asthma
2. Low exacerbation risk OR high exacerbation risk (continued exacerbations), but low blood eosinophils
   - Investigate potential cause of exacerbations, if high risk
3. Evidence for lack of efficacy of ICS (continued exacerbations)
   - If patients treated with LABA+LAMA+ICS still have exacerbations, stopping ICS may be considered [GOLD 2017]
   - Determine if there is a more appropriate therapy than ICS for lowering exacerbation risk/managing disease severity (e.g. roflumilast, macrolide)

Part 2: How to withdraw ICS in COPD patients who don’t need it

Key steps and processes

- Optimise bronchodilation with dual bronchodilation (LABA plus LAMA)
  - Initiate/continue LABA+LAMA treatment to optimise bronchodilation [Kaplan 2015; Magnussen 2014]

- Reduce ICS exposure
  - In high-dose* ICS patients, continue with lower-dose* ICS in a separate inhaler and LABA+LAMA [Kaplan 2015; Magnussen 2014]
  - In lower-dose* ICS patients, stop ICS and continue with LABA+LAMA alone [Kaplan 2015; Magnussen 2014]

- Consultation with monitoring clinician 30 days after ICS stepdown/discontinuation (including assessment of pulmonary function using spirometry)
  - Patients should be encouraged to contact their physician should their condition worsen and/or an exacerbation occur within this time

- Follow up with monitoring clinician after 6 months for full clinical review
  - See the patient twice yearly during the first year of ICS withdrawal. Patient should be encouraged to contact the physician earlier should their condition worsen and/or an exacerbation occur within this time [Kaplan 2015]
  - Follow with an annual review if the patient’s COPD is stable and exacerbation-free [Kaplan 2015]

- Reassess potential for ICS use, if moderate or severe exacerbations occur, airflow limitation worsens or blood eosinophils become elevated
  - COPD exacerbation following ICS withdrawal does not necessarily indicate a causal effect.
    - In the FLAME study, similar proportions of patients in each arm (IND/GLY and SFC) were receiving ICS prior to the study [56%]; during the study, despite no longer receiving ICS, the rate of moderate or severe COPD exacerbations was 17% lower with IND/GLY group than SFC (rate ratio, 0.83; 95% CI, 0.75 to 0.91; P<0.001) [Medicago 2016]
    - Investigate potential cause of exacerbations (e.g. ??)
    - Determine if there is a more appropriate therapy than ICS for lowering exacerbation risk/managing disease severity (e.g. roflumilast, macrolide) [Spencer 2011; GOLD 2017]
  - If necessary, continue ICS treatment in combination with appropriate long-acting bronchodilation (monitor for potential ICS-related adverse events)
    - In WISDOM, ICS withdrawal reduced trough FEV1 by 38 ml vs continuation at Week 18 (p<0.001), and by 43 ml at Week 52 [Magnussen 2014], suggesting little effect of ICS withdrawal on rate of decline.
      - This change in FEV1 did not appear to be associated with exacerbations [Magnussen 2014].
      - In clinical trials, the MCID of 100 ml is commonly used to indicate efficacy [Jones 2014]
    - If necessary, continue ICS treatment in combination with appropriate long-acting bronchodilation (monitor for potential ICS-related adverse events)
    - In WISDOM, ICS withdrawal reduced trough FEV1 by 38 ml vs continuation at Week 18 (p<0.001), and by 43 ml at Week 52 [Magnussen 2014], suggesting little effect of ICS withdrawal on rate of decline.
      - This change in FEV1 did not appear to be associated with exacerbations [Magnussen 2014].
      - In clinical trials, the MCID of 100 ml is commonly used to indicate efficacy [Jones 2014]
    - Eosinophil count should be reassessed after 9-months [Wazz 2016]
      - Increase of >300 cells/µL

*Commonly prescribed ICS treatments for COPD and recommended ICS in a separate inhaler for change in treatment

<table>
<thead>
<tr>
<th>Current treatment</th>
<th>Switch to</th>
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<tbody>
<tr>
<td>Budesonide/formoterol</td>
<td>LABA/LAMA plus budesonide 200 µg 1 puff twice daily</td>
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<tr>
<td>Fluticasone/salmeterol</td>
<td>LABA/LAMA plus fluticasone 250 µg 1 puff twice daily</td>
</tr>
<tr>
<td>Beclomethasone/formoterol</td>
<td>LABA/LAMA plus beclomethasone 100 µg 2 puffs twice daily</td>
</tr>
<tr>
<td>Fluticasone/vilanterol</td>
<td>LABA/LAMA plus fluticasone 92 µg 1 puff twice daily</td>
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References


