A GUIDE TO

deprescribing

INHALED CORTICOSTEROIDS

KEY POINTS

Long-acting muscarinic antagonists (LAMA) and long-acting beta agonists (LABA) are considered first-line treatment, to optimise bronchodilation.

Inhaled corticosteroids (ICS) reduce COPD exacerbations in high-risk patients (e.g. history of frequent exacerbations/severe COPD) or those with concomitant asthma and may improve symptoms and quality of life for some patients with COPD

ICS are not recommended in patients with COPD who are at low risk of exacerbations or who have mild disease

ICS are overprescribed in COPD and many people with COPD remain on ICS without indication or beneficial response.

Regular ICS use is associated with a dose-dependent increased risk of pneumonia, and likely impaired glucose tolerance and fracture risk. The risk of pneumonia appears to be highest among patients with more severe COPD.

Inflammatory biomarkers such as serum eosinophil count may help identify patients who are likely to benefit from ongoing ICS. Patients with eosinophil counts <100 cells/μL are unlikely to respond favourably to ICS.

Dose reduction or cessation of ICS could be considered in patients with well-controlled symptoms, ≤ 1 moderate exacerbation per year, and serum eosinophil count <300 cells/μL.

Withdrawal of ICS in appropriate patients is not associated with increased exacerbations.

deprescribing
FOR BETTER HEALTH OUTCOMES

CONTEXT

This guide considers the use of inhaled corticosteroids in adult patients with COPD, and without underlying asthma.

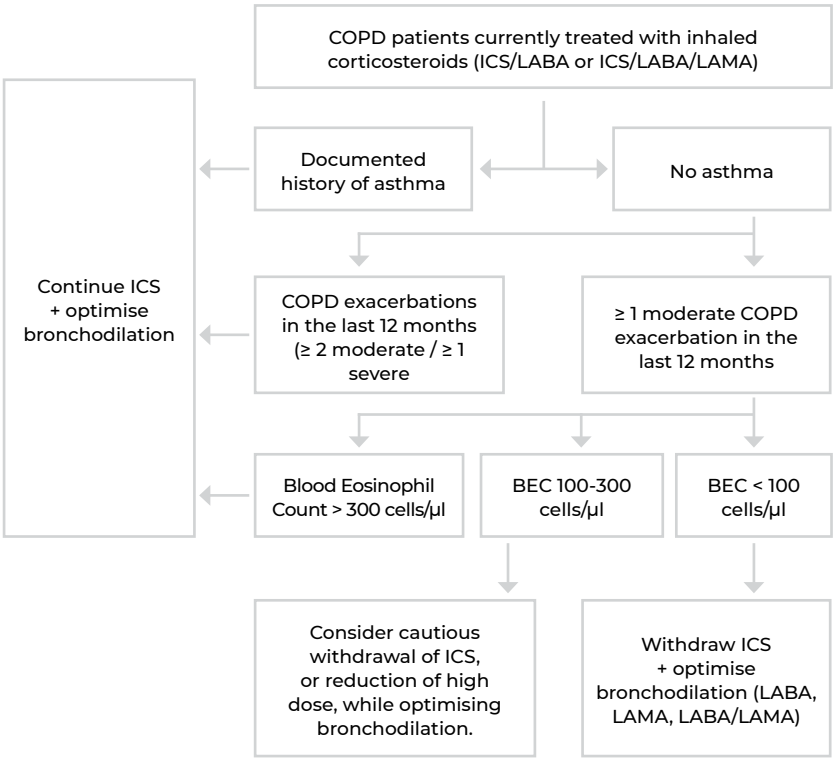
BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
Main Benefits Reduction risk of exacerbations	**Increased Benefit** • Frequent exacerbations (≥2 moderate, or 1 hospitalisation) • Presence of asthma • Blood eosinophil count >300 cells/μL	**Decreased Benefits** • <2 moderate exacerbations in the last year (<1 severe) • Blood eosinophil count <100 cells/μL
Main Harms Increased adverse effects (most seriously pneumonia)	**Reduced Harm** • Appropriate reduction of high ICS doses • Assessing inhaler technique • Encouraging spacers (where possible) and oral rinsing	**Increased Harms** • History of pneumonia infections • History of mycobacterial infections

RECOMMENDED DEPRESCRIBING STRATEGY

- Determine key aspects pf the patient's COPD history
  - Frequency and severity of exacerbations
  - Possibility of underlying asthma
  - Blood eosinophil count
- If <2 exacerbations (or <1 exacerbation resulting in hospitalisation) in the last 12 months, and eosinophil count <300 cells/μL, then consider ICS withdrawal.
- Consider reducing high-dose ICS to lower dose initially or cease low to moderate doses.
- Ensure adequate use of at least one long-acting bronchodilator (LABA or LAMA) or combination LAMA/LABA.
- Assess inhaler technique, and offer recommended vaccinations, smoking cessation, and pulmonary rehabilitation.
- Review the patient within 2-4 weeks. If symptomatic (e.g. persistent breathlessness) optimise bronchodilation, then consider other long-term therapies (e.g. antibiotics). If experiencing frequent exacerbations post-ICS cessation, assess inhaler technique and treatment adherence, and restart ICS if needed.

An Algorithm for the deprescribing of inhaled corticosteroids is shown in **Figure 1**.



NB: An exception is with history of exacerbation but BEC <100, where there is likely little benefit of ICS.

Figure 1: A potential algorithm for deprescribing inhaled corticosteroids.[15,20,32]

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a progressive lung condition characterised by airway inflammation and limitation that is not fully reversible. The defining symptoms of cough, sputum production, and dyspnoea usually do not emerge until there is significant lung damage, commonly following substantial irritant exposure. The prevalence increases with age, and it is estimated that around 7% of the population aged >65 years has COPD in Australia but may potentially be much higher given spirometry is required to confirm diagnosis.[1,2]

The management of COPD involves both symptom control, as well as prevention of acute exacerbations that accelerate disease progression, morbidity, and mortality.[3] Inhaled corticosteroids (ICS) are a component of inhaled management of COPD and were initially used based on the clinical response seen in asthma. However, recommendations for use of ICS in COPD are evolving as greater evidence emerges about appropriate therapeutic doses and potential for adverse events (e.g. pneumonia). A stepwise approach to the use of inhaled therapy is recommended for COPD, with ICS usually added when patients are already receiving a combination of a long-acting muscarinic antagonist (LAMA) and long-acting beta-agonist (LABA). The role of LAMA/LABA dual therapy has grown in recent years based on the strong evidence base for this combination and the introduction of newer LAMAs and LABAs, some of which have a faster onset of action and increased duration of therapeutic effect.

Multiple studies have shown that ICS remain over-prescribed, with a larger proportion of the COPD population using ICS than would be expected according to the stepwise titration recommended by GOLD guidelines and the Australian COPD-X Plan.[4,5]

In addition to inhaled therapy, key management strategies for COPD continue to be smoking cessation, vaccination (pneumonia, influenza, and COVID-19), and pulmonary rehabilitation.[6,7]

Current references, such as the GOLD guidelines, define moderate exacerbations of COPD as those needing oral steroids and/or antibiotics, while a severe exacerbation is one that results in hospitalisation or death.[3] Frequency of exacerbations increases with worsening COPD and the greatest risk factor for future COPD exacerbations, is a previous history of exacerbations, particularly in the last 12 months.[8,9]

EFFICACY

The evidence for inhaled corticosteroids is predominantly from trials of single ICS or ICS /LABA combinations, versus placebo or a bronchodilator (LABA or LAMA). High dose ICS therapy has typically been used in patients with moderate to severe COPD. Inhaled corticosteroids (ICS) have been shown to improve symptoms and quality of life, as well as reduce the rate of moderate to severe (but not mild) exacerbations. There tend to be small reductions in decline of lung function (Forced expiratory volume in the first second, FEV1), and mortality benefit has only been seen with recent trials.[10]

Cochrane meta-analyses of ICS vs LABA randomised-controlled trials (RCTs) found that bronchodilators improved lung function more than ICS. ICS use was associated with a reduction in exacerbation rate and improvement in quality of life, though at a cost of higher rates of adverse events such as pneumonia.[11,12] The focus for ICS therapy has now largely shifted towards their greater benefits for reductions of moderate to severe exacerbations, especially given the importance of exacerbations for worsening lung function and mortality. Most trials of ICS/LABA combinations versus LABA alone have found the rate of moderate to severe exacerbations was reduced by 25-35%.[13]

Similar results are seen in comparisons with the long-acting muscarinic antagonists (LAMA). FLAME compared ICS/LABA to LAMA/LABA. Those without asthma or frequent exacerbations (i.e. at low risk of exacerbations), had less exacerbations on the LAMA/LABA combination.[14] Meanwhile TRIBUTE found that in a population with severe COPD and a history of exacerbations, a step-up from their LAMA/LABA to triple therapy (i.e. addition of ICS) was associated with a reduction of exacerbations by around 15% (NNT of 12).[9]

The IMPACT study compared triple therapy (fluticasone furoate/umeclidinium/ vilanterol) against LAMA/LABA and ICS/LABA combinations, in COPD patients at a higher risk of exacerbations.[15] The 10,355 participants had either an FEV1 <50% and one recent moderate/severe exacerbation, or a FEV1 of 50-80% with at least two moderate (or one severe) exacerbation in the last year.

The primary outcome was the rate of moderate or severe exacerbations during treatment (12 months). Triple inhaler therapy was associated with a 15% reduction in exacerbation rate compared to the ICS/ LABA combination, and a 25% reduction compared to the LAMA/LABA. Compared to LAMA/LABA, the triple therapy inhaler would prevent one annual moderate or severe exacerbation per 10 people treated and prevent one annual severe exacerbation per 20 people.

This comes at the cost of one extra case of pneumonia for every 35 people.[8,16]

This was reinforced by the results of ETHOS, with triple therapy (both higher and lower budesonide doses) compared to ICS/LABA and LAMA/LABA combination in a similar population with more severe COPD and recent exacerbations. Reductions in the rate of moderate-severe exacerbations were 14% vs ICS/LABA (NNT=7) and 25% vs LAMA/LABA (NNT=3) respectively. An analysis of mortality outcomes in ETHOS found a reduction in death from cardiovascular causes with corticosteroid use (0.5% with high dose budesonide vs 1.4% with LAMA/LABA), a reduction of 49% in mortality (NNT of 80). ICS use was associated with increased rates of pneumonia (NNH of 58).[17]

The greatest reduction in mortality and exacerbation rate with ICS is seen in those with moderate to severe COPD and a history of exacerbation in the last 12 months, as well as in those with higher serum eosinophil levels. While a decrease in exacerbations is seen with the addition of ICS (i.e. triple therapy), no difference in exacerbation rate has been seen in the trials where corticosteroids were withdrawn (e.g. WISDOM and SUNSET, see Withdrawal of ICS).[18] Given that there are numerous variations in COPD pathophysiology itself, the varied response to ICS in some populations, and the risk of adverse effects, identifying who will most benefit from corticosteroid use is fundamental to principles of best practice and quality use of medicines.

SERUM EOSINOPHIL LEVELS

To help identify the patients most likely to benefit from ICS there is increasing interest in the use of inflammatory biomarkers in COPD, particularly measuring blood eosinophil counts (BEC). Its use as a prognostic marker to predict COPD exacerbations is debated, however there is growing evidence that it appears useful in assessing the potential response and efficacy of inhaled corticosteroids when added to LAMA and/or LABA.[3,19]

Lung inflammation in COPD is predominantly driven by neutrophils, as opposed to the eosinophilic inflammation seen in asthma. However, in COPD patients with more frequent exacerbations there is an association with higher sputum eosinophil levels, which may partly explain the increased benefit of oral and inhaled corticosteroids in this population.[20,21] Studies have linked elevated sputum eosinophils with elevated serum levels (blood eosinophil count, BEC) and multiple post-hoc analyses of trials have found a gradient of higher rates of exacerbation with greater elevations of serum eosinophils.[20,23]

Note, when referring to serum eosinophil levels, literature tends to refer to cells/microlitre, such as 300 cells/μL, while SI units are typically reported in Australian pathology, where an equivalent would be 0.3 x 109/L (or 0.3/nL). Some studies report eosinophil levels by percentage of overall white cell count, where cut-offs of <2% and >2% are often used to refer to low and high levels respectively.[24]

A 2018 meta-analysis of 14 studies (16,751 patients) analysed the rate of moderate and severe exacerbations, change in FEV1, and rate of pneumonia of triple therapy (ICS/LAMA/LABA) versus LAMA/LABA versus single LABA or LAMA.[25] Triple therapy was found to reduce the rate of exacerbations and improve FEV1 compared to LAMA/LABA (RR 0.70, 95% CI 0.53-0.94, annual NNT=38). Exacerbation rate was significantly higher in those with a blood eosinophil count ≥300 cells/μL following corticosteroid removal (RR 0.57, 95% CI 0.48-0.68, annual NNT=9), whereas there was less of an impact when ceasing ICS in patients with eosinophil count <300 cells/μL (annual NNT=~46).

While trials have used different cut-offs establishing low versus high eosinophil levels, there appears to be marked thresholds with consensus regarding ICS effect. COPD patients with levels <100 cells/μL do not appear to respond to ICS use, regardless of disease severity or exacerbation rate, whereas those where baseline or current BEC remains ≥300 cells/μL have a clear increase in risk and benefit from ICS and are strongly recommended to remain on inhaled corticosteroid therapy. For BEC between these numbers, clinical factors are recommended to be considered on an individual basis, remembering that the definitions are not necessarily clear as cell counts fluctuate.[16]

Serum eosinophils (cell/μL)	Inhaled corticosteroid use recommended	
<100	No	
100-300	Factors against:	1-2 moderate exacerbations
		Exacerbations responding to antibiotics
		Current smoker
	Factors for:	>2 moderate or 1 severe exacerbation
		Response from oral corticosteroids for exacerbations
		Former smoker
>300	Yes	

Table 1: Recommended BEC cut-offs for use of inhaled corticosteroids, with factors to help guide decision-making. Based on secondary analysis of IMPACT by Stolz et al.[16]

COVID AND INHALED CORTICOSTEROIDS

COVID-19 is suspected to involve initial viral infection and replication, that leads to a dysregulated immune response often involving excessive inflammatory mediators. This hyperinflammation is thought to be a key factor in disease severity and death. Reducing this inflammation may reduce disease progression and severity, however, there has been concern that immunosuppression (e.g. steroid use) may increase the initial viral replication.[43]

At present, there is no clear evidence that inhaled therapies can reduce the risk of developing COVID-19 or modify disease progression. The latest GOLD guidelines recommend that COPD patients who develop COVID continue on their standard inhaled therapy, regardless of whether that includes inhaled corticosteroids or not.[3]

Early use of inhaled corticosteroids may reduce hospitalisation in patients with mild COVID not requiring oxygen therapy. This is predominantly based on the PRINCIPLE trial, which compared inhaled budesonide with usual care (noting that people already taking inhaled corticosteroids were excluded). Inhaled budesonide 800microgram BD for 14 days led to a lower rate of hospitalisation (Odds Ratio 0.75, 95% CI 0.55-1.03). Overall, there is only moderate quality evidence from 4 studies involving 2335 participants, that inhaled corticosteroids (budesonide or ciclesonide) may reduce hospitalisation (RR 0.64, CI 95% 0.31-1.30).[44]

Current Australian guidelines recommend that inhaled corticosteroids (budesonide or ciclesonide) be considered within 14 days of symptom onset in adults with COVID-19 who do not require oxygen therapy and with a risk factor for disease progression (such as COPD or age >65 years).[46]

EVIDENCE FOR WITHDRAWING ICS

A notable trial from 2014, WISDOM, looked at the stepwise deprescribing of ICS in patients with severe COPD (FEV1 <50%) and a history of recent exacerbations (at least one in the last 12 months) who were on ICS/LAMA/LABA combinations. Patients in the deprescribing group had high-dose fluticasone propionate (500 micrograms BD) reduced every 6 weeks until withdrawn, remaining on combined LAMA/LABA therapy (salmeterol/tiotropium). Over the 12-month study there was a small decrease in lung function (FEV1 reduced by 38mL at 18 weeks), though no increase in the primary outcome of moderate-severe exacerbations following ICS withdrawal (RR=1.06, 95% CI 0.94-1.19)[26] (see **Figure 2**). A post-hoc analysis of eosinophil level subsets, found no change in exacerbation rate following withdrawal for those with BEC <300 cells/µL (RR 1.04, 95% CI 0.89-1.21, p=0.59).[27]

A 2020 European Respiratory Society Guideline about withdrawing ICS was based on a meta-analysis of four major trials (COSMIC, INSTEAD, WISDOM, SUNSET).[28] These trials all compared deprescribing of ICS versus continuing ICS in stable COPD patients, with the ICS replaced with alternate long-acting bronchodilator therapy (LABA or LAMA or both). Deprescribing ICS did not result in an increase in moderate or severe exacerbations, either in frequency (RR 1.05, 95% CI 0.97-1.13) or in time to first exacerbation (HR 1.04, 95% CI 0.94-1.16). In addition, the guideline made the following recommendations:

- Conditional recommendation for the withdrawal of ICS in patients without a history of exacerbations,
- Strong recommendation for maintaining ICS in patients with elevated eosinophils (BEC ≥300 cells/µL) regardless of exacerbation history
- Strong recommendation for ensuring long-acting bronchodilators are used if ICS are withdrawn.

Different COPD-severity populations were studied in the above trials. For instance, SUNSET and INSTEAD had patients at low risk for exacerbations (none in the previous year), while WISDOM and COSMIC had populations of greater severity and frequent exacerbations. Patients in INSTEAD were managed with a sole long-acting bronchodilator, while the others resulted in patients switching to LAMA/LABA combinations, and this approach seems reasonable when planning to withdraw a patient's ICS.[29]

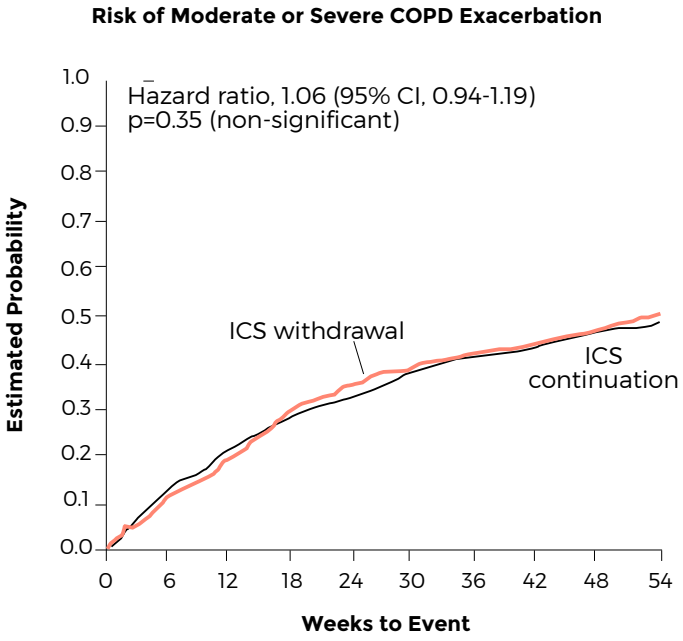


Figure 2 : Estimated probability ofmoderate or severe exacerbation rate with ICS withdrawal, from WISDOM trial[26]

Multiple trials and groups have developed algorithms to assess the use of ICS in COPD patients, and how to enact drug withdrawal. A review by Avdeev et al. compared several strategies, particularly those emerging from trials such as WISDOM. The common factors for most include assessing history and presence of concomitant asthma, exacerbation frequency and severity, and blood eosinophil levels. Some algorithms have included symptom severity/FEV1. For patients with poor symptom control and lung function in the absence of exacerbations, long-acting bronchodilators are preferred to long-term ICS.[30]

Medicines	Class	Inhaler	Inhaler Type	Typical Dose (inhalations)	Total daily ICS dose (microgram)
High Dose ICS regimen (consider reducing ICS dose or swap to LAMA/LABA)					
fluticasone propionate 500microgram with salmeterol 50microgram	ICS/LABA	Seretide 500/50, Pavtide 500/50 Accuhaler	DPI	1 BD	1000
fluticasone propionate 250microgram with salmeterol 25microgram	ICS/LABA	Seretide 250/25, Pavtide 250/25	pMDI	2 BD	1000
Medium Dose ICS regimen (consider swapping to LAMA/LABA)					
fluticasone furoate 100microgram with umeclidinium 62.5microgram/ vilanterol 25microgram	ICS/LAMA/ LABA	Trelegy Ellipta	DPI	1 daily	100
beclometasone 100microgram with glycopyrronium 10microgram/ formoterol 6microgram	ICS/LAMA/ LABA	Trimbow	pMDI	2 BD	400
budesonide 160microgram with glycopyrronium 7.2microgram/ formoterol 5microgram	ICS/LAMA/ LABA	Breztri Aerosphere	pMDI	2 BD	640
budesonide 400microgram with formoterol 12microgram	ICS/LABA	Symbicort Turbuhaler 400/12, DuoResp Spiromax 400/12	DPI	1 BD	800
budesonide 200microgram with formoterol 6microgram	ICS/LABA	Symbicort Rapihaler 200/6	pMDI	2 BD	800
fluticasone furoate 100microgram with vilanterol 25microgram	ICS/LABA	Breo Ellipta	DPI	1 daily	100
Not covered by the PBS (may be TGA approved) for COPD					
fluticasone propionate 250microgram with salmeterol 50microgram	ICS/LABA	Seretide 250/50, Pavtide 250/ Accuhaler	DPI	1 BD	500
fluticasone propionate 125microgram with salmeterol 25microgram	ICS/LABA	Seretide 125/25, Pavtide 125/25	pMDI	2 BD	500
budesonide 200microgram with formoterol 6microgram	ICS/LABA	Symbicort Turbuhaler 200/6, DuoResp Spiromax 200/6	DPI	1 BD	400
beclometasone 100mcg/ formoterol 6mcg	ICS/LABA	Fostair	pMDI	2 BD	400
LAMA/LABA combination inhalers (non-ICS containing)					
umeclidinium 62.5microgram/ vilanterol 25microgram	LAMA/LABA	Anoro Ellipta	DPI	1 daily	
glycopyrronium 50microgram/ indacaterol 110microgram	LAMA/LABA	Ultibro Breezhaler	Capsule DPI	1 daily	
tiotropium 2.5microgram/olodaterol 2.5microgram	LAMA/LABA	Spiolto Respimat	Soft Mist Inhaler	2 mane	
aclidinium 340microgram/formoterol 12microgram	LAMA/LABA	Brimica Genuair	DPI	1 BD	

This table represents combination inhalers and doses indicated for COPD as of October 2022. Higher and lower doses of some inhalers are approved for asthma. The use of ICS-alone inhalers is not recommended in COPD. This table does not show ICS potency equivalence. Categories of high and medium ICS dose are from labels used in GINA asthma guidelines based on product information.

Table 2: Combination inhalers being used for COPD management in Australia as of October 2022.

ADVERSE EFFECTS

There is good evidence that ICS use increases oropharyngeal adverse effects (e.g. oral candidiasis and dysphonia) as well as systemic effects of skin bruising and pneumonia. Observational evidence suggests associations with other respiratory infections, diabetes, bone effects/fractures, and cataracts.[3,32]

The COPD population is typically an older population with multiple comorbidities and increased frailty and has been shown to experience a higher incidence of adverse effects from inhaled corticosteroid use.[9] If patients must continue using ICS, ensuring adequate inhaler technique, encouraging spacer devices where appropriate, and oral rinsing/spitting after ICS use are strategies to help reduce some adverse effects. Evidence suggests that almost 1 in 3 Australian patients who use ICS do not have a rinsing procedure which is likely to optimally eliminate oropharyngeal drug residues.[31]

PNEUMONIA

Pneumonia is more frequent in COPD patients and smokers; however, the use of ICS further increases the risk. This is well established, as is the association of pneumonia rates with higher doses of ICS and particular corticosteroids within the class.[32]

A 2014 Cochrane Review (meta-analysis of 43 studies) reinforced the increased risk of pneumonia with use of ICS, both when used alone or in combination.[33] An increased rate of serious pneumonia requiring hospitalisation was found for both corticosteroids involved in the trials, fluticasone (OR 1.78, 95%CI 1.50 to 2.12) and budesonide (OR 1.62, 95% CI 1.00 to 2.62). This relates to 18 more cases of serious pneumonia for every 1000 fluticasone users over 18 months, and an additional 6 serious pneumonia cases per 1000 budesonide-users over 9 months. The study was not able to find a statistical difference between the two agents, though did find lower rates of pneumonia with lower vs higher doses of budesonide.

A large Canadian population-based observational study (103,386 ICS-users between 1999-2005) found that ICS discontinuation was associated with a significant 37% reduction (RR 0.63, 95% CI, 0.60-0.66) in the incidence of serious pneumonia leading to hospitalisation or death.[34] This risk reduction was seen soon after corticosteroid cessation with a 20% decrease at one month and a 50% decrease at 4 months. Greater risk reduction was seen in patients using fluticasone propionate (RR, 0.58; 95% CI, 0.54-0.61) compared to budesonide (RR, 0.87; 95% CI, 0.78-0.97).

MYCOBACTERIAL INFECTIONS

Evidence suggests that inhaled corticosteroid use increases the risk of non-tuberculosis mycobacterial infections. A 2012 population study found patients with COPD had a 15.7-fold increased risk of mycobacterial infections in general, with a marked difference depending on use of inhaled corticosteroids or not (Odds Ratio of 29.1 vs 7.6 respectively) and between low and high dose ICS (Odds Ratio 28.1 vs 47.5 respectively).[35] A further 2017 study by Brode et al., found an increase in non-tuberculosis mycobacterial infections associated with ICS use (aOR 1.86, 95% CI 1.6-2.15). Higher rates were seen with dose escalation as well as cumulative dose of inhaled corticosteroids.[36]

LOCAL ORAL EFFECTS

Inhaled corticosteroids result in an increase in local oral adverse effects. A 2012 Cochrane review found ICS use was associated with an increase in oropharyngeal candidiasis (OR 2.65, 95% CI 2.03 to 3.46, 5586 participants and dysphonia/hoarseness (OR 1.95, 95% CI 1.41 to 2.70, 3267 participants) in trials with greater than six-month's ICS use. Patients on <1000micrograms of budesonide (equivalent to ~500microgram fluticasone propionate) had a NNH of 37. Oral adverse effects have been seen within 4 weeks of ICS use in trials with high doses.[11]

Evidence supports that oral adverse effects are dose related, more likely with fluticasone than budesonide, and possibly less common with dry-powder inhalers compared to metered-dose inhalers.[37,38]

SKIN BRUISING

Pooled data from studies involving 5073 people found an increased incidence of skin bruising with ICS use (RR 1.63, 95% CI 1.31-2.03).[11]

DIABETES

In COPD patients with diabetes, there is some evidence to support a direct relationship between ICS dose and blood glucose levels.[39]

This was further supported by the results of a large Cohort study from Canada that found the use of inhaled corticosteroids was associated with an increased risk of diabetes (the use of initial diabetic therapy, HR 1.34, 95% CI 1.29-1.39) and an increased rate of diabetes progression (initiation of insulin, HR 1.34, 95% CI 1.17-1.53). These outcomes increased with higher doses of ICS, particularly in those on high doses of fluticasone (1500-2000microgram daily).[40]

OSTEOPOROSIS

A 2011 meta-analysis found significant increased risks of bone fracture from both RCTs (17,500 participants, OR 1.27; 95% CI 1.01 to 1.58) and observational studies (69,000 participants, OR 1.21; 95% CI 1.12 to 1.32).[41] The majority of trials involved fluticasone propionate in long-term users (mean 90 weeks), and a dose-response was seen in the observational data.

A further meta-analysis however failed to find any significant difference in bone fracture with ICS use up to 3 years compared to placebo.[11]

A Swedish cohort study in 2021 (9651 participants) comparing people with COPD versus people without, indicated that those COPD patients on higher dose ICS had an increased risk of bone fracture (RR 1.52, 95% CI 1.24-1.62).[42]

While the evidence is unclear, this suggests caution with ICS use in older, frail COPD patients with osteoporosis.

FACTORS TO CONSIDER

IN FAVOUR OF DEPRESCRIBING

- High-dose ICS could be reviewed and likely reduced in dose for most patients with COPD, as high dose ICS provide no greater benefit compared with low-moderate ICS doses. In patients with poor inspiratory flow or poor hand-lung coordination, a change in inhaler device or use of a spacer could improve lung deposition, allowing for a decrease in ICS dose.
- Deprescribing may be appropriate for those experiencing adverse effects, particularly recurrent episodes of pneumonia or a history of mycobacterial infections.
- Many patients may have started ICS using a ICS/LABA combination before LAMA/LABA inhalers became preferred therapy based on more recent studies. These patients and those without a clear indication for ICS use are often suitable targets for reviewing and deprescribing of ICS.
- There is strong support for absence of ICS benefit in patients without a history of exacerbations, and cessation is appropriate. In those with infrequent exacerbations, optimising bronchodilators (e.g. change to LAMA/LABA) may provide adequate COPD control and could be assessed for potential ICS deprescribing. Eosinophil count <100 cells/µL regardless of exacerbation frequency, is an indicator of absence of benefit from inhaled corticosteroid use.

AGAINST DEPRESCRIBING

- In COPD patients who also have a history of asthma the use of ICS is recommended given a greater degree of eosinophilic inflammation. An ICS/LABA is considered first line therapy rather than a LAMA/LABA.
- Continued use of inhaled corticosteroids is recommended in those with high eosinophil counts and/or frequent exacerbations: ≥2 moderate exacerbations of ≥1 severe exacerbation (hospitalisation) per year.
- Patients with eosinophil count >300 cells/µL should remain on inhaled corticosteroids regardless of exacerbation history.
- Evidence is less clear when blood eosinophils are between 100 to 300 cells/µL. Ongoing ICS use is recommended if there is a recent history of exacerbations (moderate or severe), ensuring adequate bronchodilator therapy (likely LAMA/LABA combination).

DISCONTINUATION SYNDROMES

While in the WISDOM trial fluticasone was decreased gradually over a 12-week period, other major trials have had patients cease ICS immediately, without any concerns or adverse events.[28] This suggests that abrupt cessation or switching of inhaled agents may be suitable. Initial reduction of high-dose ICS could be considered as a cautious approach, particularly for those with higher eosinophil levels (see **Table 2**). Guidelines recommend optimisation of bronchodilators (LABA and/or LAMA) with cessation of inhaled corticosteroids.[3]

REFERENCES

1. Australian Institute of Health and Welfare 2020. Chronic obstructive pulmonary disease (COPD). Cat. no. ACM 35. Canberra: AIHW. Viewed 26 May 2021, https://www.aihw.gov.au/reports/chronic-respiratory-conditions/copd
2. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007;370(9589):741-750.
3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease-2022 report. November 2021.
4. Price D, West D, Brusselle G, et al. Management of COPD in the UK primary-care setting: an analysis of real-life prescribing patterns. Int J Chron Obstruct Pulmon Dis. 2014;9:889-904. Published 2014 Aug 27.
5. Rinne ST, Wiener RS, Chen Y, et al. Impact of Guideline Changes on Indications for Inhaled Corticosteroids among Veterans with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2018;198(9):1226-1228. doi:10.1164/rccm.201803-0554LE
6. Yang IA, George J, McDonald CF, McDonald V, O'Brien M, Smith B, McNamara R, Zwar N, Dabscheck E. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2021. Version 2.64, June 2021.
7. Riley CM, Sciurba FC. Diagnosis and Outpatient Management of Chronic Obstructive Pulmonary Disease: A Review. JAMA. 2019;321(8):786-797.
8. Halpin DMG, Dransfield MT, Han MLK, et al. The effect of exacerbation history on outcomes in the IMPACT trial. Eur Respir J 2020; 55: 1901921
9. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363(12):1128-1138.
10. Tantucci C, Pini L. Inhaled Corticosteroids in COPD: Trying to Make a Long Story Short. Int J Chron Obstruct Pulmon Dis. 2020;15:821-829. Published 2020 Apr 20.
11. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012;2012(7):CD002991.
12. Spencer_S, Karner_C, Cates_CJ, Evans_DJ. Inhaled corticosteroids versus long-acting beta2-agonists for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD007033.
13. Agusti A, Fabbri LM, Singh D, et al. Inhaled corticosteroids in COPD: friend or foe?. Eur Respir J. 2018;52(6):1801219. Published 2018 Dec 13.
14. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Engl J Med. 2016;374(23):2222-2234. doi:10.1056/NEJMoa1516385
15. Lipson DA, Barnhart F, Brealey N, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med. 2018;378(18):1671-1680.

16. Stolz D, Miravitlles M. The right treatment for the right patient with COPD: lessons from the IMPACT trial. Eur Respir J. 2020;55(5):2000881. Published 2020 May 21.
17. Martinez FJ, Rabe KF, Ferguson GT, et al. Reduced All-Cause Mortality in the ETHOS Trial of Budesonide/Glycopyrrolate/Formoterol for Chronic Obstructive Pulmonary Disease. A Randomized, Double-Blind, Multicenter, Parallel-Group Study. Am J Respir Crit Care Med. 2021;203(5):553-564.
18. Koarai A, Yamada M, Ichikawa T, Fujino N, Kawayama T, Sugiura H. Triple versus LAMA/LABA combination therapy for patients with COPD: a systematic review and meta-analysis. Respir Res. 2021;22(1):183. Published 2021 Jun 22.
19. International Primary Care Respiratory Group. Appropriate use and withdrawal of inhaled corticosteroids (ICS) in patients with chronic obstructive pulmonary disease (COPD). DESKTOP HELPER No. 6 2nd edition May 2020
20. Brightling CE, Monteiro W, Ward R, et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2000; 356: 1480–1485.
21. Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med. 2011;184(6):662-671.
22. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials [published correction appears in Lancet Respir Med. 2015 Jun;3(6):e19]. Lancet Respir Med. 2015;3(6):435-442.
23. Siddiqui SH, Pavord ID, Barnes NC, et al. Blood eosinophils: a biomarker of COPD exacerbation reduction with inhaled corticosteroids. Int J Chron Obstruct Pulmon Dis. 2018;13:3669-3676. Published 2018 Nov 6.
24. Pavord ID, Jones PW, Burgel PR, Rabe KF. Exacerbations of COPD. Int J Chron Obstruct Pulmon Dis. 2016;11 Spec Iss(Spec Iss):21-30. Published 2016 Feb 19. doi:10.2147/COPD.S85978
25. Cazzola M, Rogliani P, Calzetta L, Matera MG. Triple therapy versus single and dual long-acting bronchodilator therapy in COPD: a systematic review and meta-analysis. Eur Respir J. 2018;52(6):1801586. Published 2018 Dec 13.
26. Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. N Engl J Med. 2014;371(14):1285-1294.
27. Watz H, Tetzlaff K, Wouters EF, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. Lancet Respir Med. 2016;4(5):390-398.
28. Chalmers JD, Laska IF, Franssen FME, et al. Withdrawal of inhaled corticosteroids in COPD: a European Respiratory Society guideline. Eur Respir J. 2020;55(6):2000351. Published 2020 Jun 4. doi:10.1183/13993003.00351-2020
29. Cataldo D, Derom E, Liistro G, et al. Overuse of inhaled corticosteroids in COPD: five questions for withdrawal in daily practice. Int J Chron Obstruct Pulmon Dis. 2018;13:2089-2099. Published 2018 Jul 5. doi:10.2147/COPD.S164259
30. Avdeev S, Aisanov Z, Arkhipov V, et al. Withdrawal of inhaled corticosteroids in COPD patients: rationale and algorithms. Int J Chron Obstruct Pulmon Dis. 2019;14:1267-1280. Published 2019 Jun 10
31. Johnstone LK, Bereznicki BJ, Jacobson G, Thompson AJ. Implementation of mouth rinsing after use of inhaled corticosteroids in Australia. Int J Clin Pharm. 2021;43(3):549-555. doi:10.1007/s11096-020-01161-7
32. Crim C, Calverley PM, Anderson JA, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. Eur Respir J. 2009;34(3):641-647.
33. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014;2014(3):CD010115. Published 2014 Mar 10.
34. Suissa S, Coulombe J, Ernst P. Discontinuation of Inhaled Corticosteroids in COPD and the Risk Reduction of Pneumonia. Chest. 2015;148(5):1177-1183.
35. Andréjak C, Nielsen R, Thomsen VØ, Duhaut P, Sørensen HT, Thomsen RW. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. Thorax. 2013;68(3):256-262.
36. Brode SK, Campitelli MA, Kwong JC, et al. The risk of mycobacterial infections associated with inhaled corticosteroid use. Eur Respir J. 2017;50(3):1700037. Published 2017 Sep 20.
37. Rachelefsky GS, Liao Y, Faruqi R. Impact of inhaled corticosteroid-induced oropharyngeal adverse events: results from a meta-analysis. Ann Allergy Asthma Immunol. 2007;98(3):225-238.
38. Dekhuijzen PNR, Batsiou M, Bjermer L, et al. Incidence of oral thrush in patients with COPD prescribed inhaled corticosteroids: Effect of drug, dose, and device. Respir Med. 2016 Nov;120:54-63.
39. Slatore CG, Bryson CL, Au DH. The association of inhaled corticosteroid use with serum glucose concentration in a large cohort. Am J Med. 2009;122(5):472-478.
40. Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. Am J Med. 2010;123(11):1001-1006.
41. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. Thorax. 2011;66(8):699-708.
42. Janson C, Lisspers K, Ställberg B, et al. Osteoporosis and fracture risk associated with inhaled corticosteroid use among Swedish COPD patients: the ARCTIC study. Eur Respir J. 2021;57(2):2000515. Published 2021 Feb 17. doi:10.1183/13993003.00515-2020
43. Agusti A, Torres F, Faner R. Early treatment with inhaled budesonide to prevent clinical deterioration in patients with COVID-19. Lancet Respir Med. 2021;9(7):682-683.
44. National COVID-19 Clinical Evidence Taskforce. Australian Guidelines for the clinical care of people with COVID-19. V58.1. Published 28/06/2022.

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