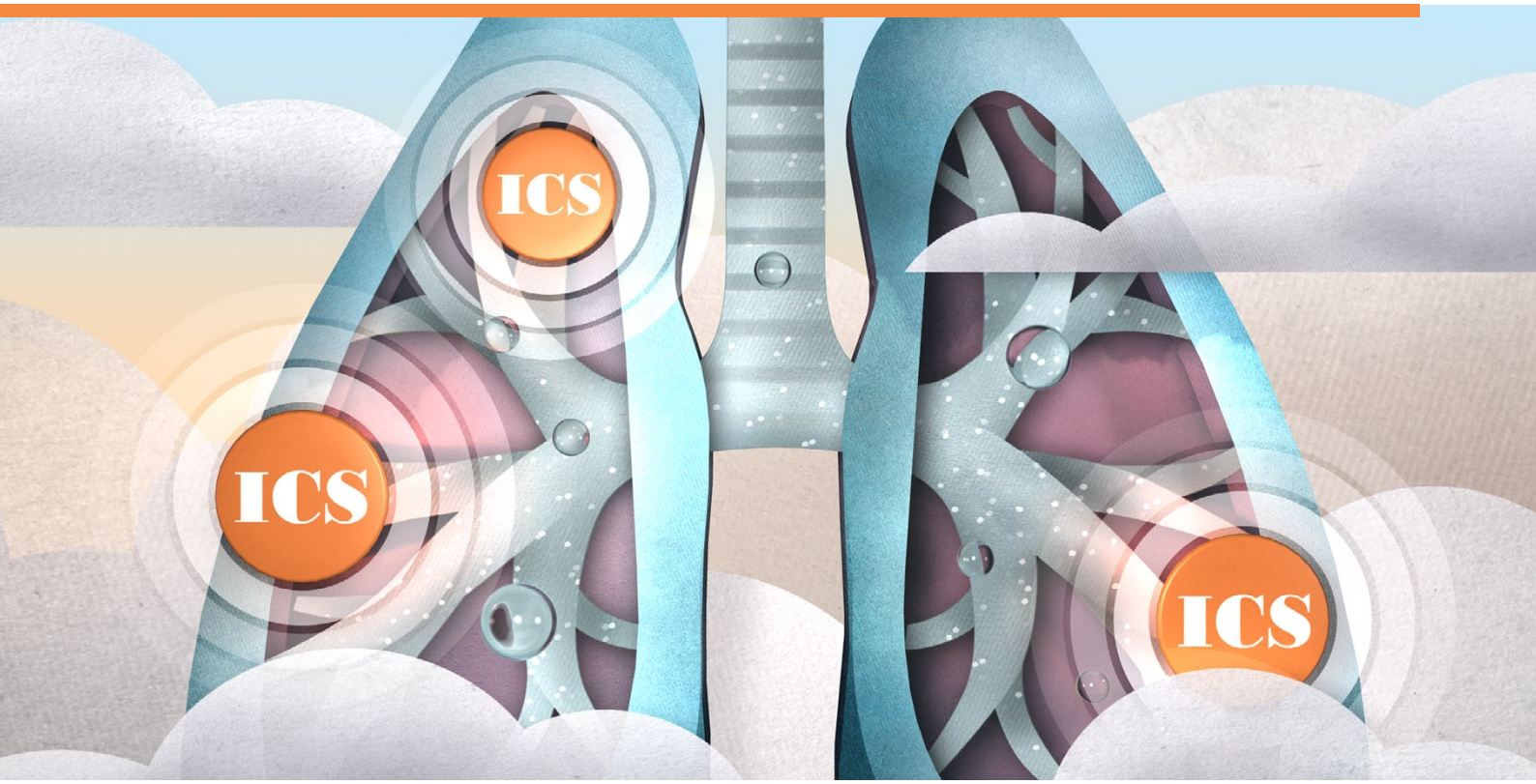

Inhaled corticosteroids for adults with asthma

A key decision in asthma management is when to initiate an inhaled corticosteroid (ICS). It is clear that patients with weekly asthma symptoms are likely to benefit from ICS treatment. However, emerging evidence suggests that patients with less frequent symptoms, e.g. monthly, will also benefit from ICS treatment, although adherence is often low in this group. It is recommended that clinicians offer an ICS to patients according to their treatment goals.

KEY MESSAGES:

- As part of the four-stage consultation framework for managing patients with asthma in primary care, pharmacological treatment is adjusted according to the patient's symptoms and risk of exacerbations (Stage three of the consultation)
- ICS are the most effective class of medicine available to control asthma symptoms and reduce exacerbation risk
- Offer an ICS to all patients who have had symptoms on two or more occasions in the past week, or an exacerbation in the past year that required oral corticosteroids. However, patients who have less frequent symptoms that they consider troublesome may also wish to begin ICS treatment.
- Daily ICS treatment can begin at a standard dose (previously referred to as low dose), i.e. 400 micrograms beclomethasone dipropionate, 200 micrograms beclomethasone dipropionate extrafine, 400 micrograms budesonide or 200 micrograms fluticasone propinonate
- A "step up" in treatment to an ICS/LABA should be considered for patients with symptoms that are not controlled by a standard ICS dose, once adherence, inhaler technique and "treatable traits" have been assessed
- A "step down" to a lower dose of an ICS may be considered for patients with well-controlled asthma who have a low risk of exacerbations

Inhaled corticosteroids underpin the pharmacological treatment of asthma

Long-term inflammation of the airways with eosinophil infiltration is a hallmark of asthma, even in patients who experience infrequent symptoms.[1] An inhaled corticosteroid (ICS) is the most practical and effective medicine to control airway inflammation, reduce symptoms and prevent exacerbations in patients with asthma.[1] Delivery by inhalation results in a higher concentration of medicine in the airways and fewer systemic adverse effects than systemic administration of corticosteroids.[2]

The mechanism of ICS action

At a molecular level an ICS switches off activated genes that encode for inflammatory proteins such as cytokines, adhesion molecules and enzymes.[1] This results in reduced eosinophil numbers in the airways and sputum, as well as reductions in the number of activated T cells and mast cells in the airway mucosa.[1] Patients with asthma may experience improvements in symptoms and lung function several days after beginning ICS treatment, however, it may take a number of months to achieve a maximal reduction in airway hyper-responsiveness.[1] Withdrawal of an ICS is often associated with a deterioration in asthma control.[1]

When to initiate an ICS

The New Zealand Asthma Guidelines recommend an ICS for patients at Step 2 in the five-step treatment model for asthma management (Figure 1).

The optimal point at which to initiate ICS treatment in patients with asthma is not conclusively known. However, following an assessment of asthma severity (Stage one of the asthma consultation), and the identification of any contributing factors (Stage two of the consultation), consideration should be given to initiating an ICS for patients not already on this treatment (Stage three of the consultation).

- The New Zealand Asthma Guidelines recommend beginning ICS treatment when patients have symptoms of asthma on two or more occasions in the previous week.[3]
- The Asthma Guidelines also acknowledge that people with less frequent symptoms may benefit from treatment with an ICS (see: "The START study").[3]
- The Global Initiative for Asthma (GINA) recommends initiating an ICS for patients with asthma who require a SABA between twice a month and twice a week or for those who wake due to asthma symptoms once a month.[2]
- If the patient has had an asthma exacerbation requiring oral corticosteroids in the past year, this also suggests that ICS treatment is appropriate.[3]

Discuss the benefits of ICS treatment and the risks

When considering initiating ICS treatment it is necessary to balance the potential benefits with the reality that adherence is often poor in people with mild asthma.[4] Some patients may judge the inconvenience of daily treatment and the possibility of adverse effects to be more important than the benefits of early ICS treatment.[5] Discuss any concerns patients might have about ICS treatment (e.g. adverse effects, "steroid stigma") and where appropriate reassure them that systemic adverse effects at standard doses are relatively uncommon (see Page 4).

A safety fact sheet for patients taking inhaled corticosteroids is available from the Asthma and Respiratory Foundation: **www.asthmafoundation.org.nz/resources/safety-of-inhaled-corticosteroids-ics**

ICS treatment begins with a trial to assess the patient's response

Treatment with an ICS should begin as a trial with the patient's response assessed at their next consultation. It is recommended that a follow-up appointment be scheduled eight weeks after ICS treatment begins.[3] Patients with mild asthma have symptoms that are well controlled with a standard daily ICS dose. Patients with moderate asthma are likely to require a step up to an ICS/LABA.[2]

Information on assessing asthma severity is available in: "Managing adults with asthma in primary care: the four-stage consultation"

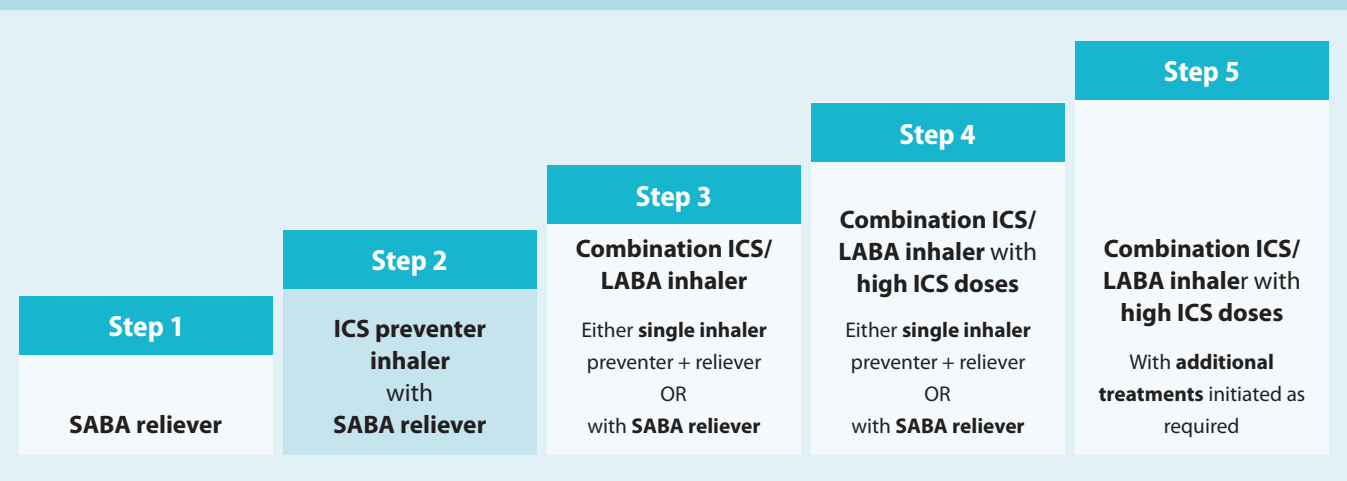

Figure 1: The stepwise treatment of adult asthma, adapted from Beasley *et al*, 2016.[3]

Which ICS regimen is most effective?

There is a lack of well designed studies comparing different types of ICS in the treatment of asthma. All ICS subsidised in New Zealand are broadly considered to be equally effective when taken at clinically equivalent doses, i.e. beclomethasone dipropionate and budesonide are approximately equivalent to fluticasone propinonate taken at half the dose.[5] Patient preference for inhaler devices and clinical experience are the main factors in determining ICS selection.

Choosing a starting dose for an ICS

Patients with asthma can begin treatment with an ICS at a standard dose (Table 1).[3] The term "standard dose" has replaced the term low dose that was used in previous guidance. Standard doses provide patients with 80 – 90% of the maximum obtainable benefit of ICS treatment.[3] It is recommended that ICS be initiated with twice daily dosing, as this is slightly more effective than once daily dosing.[5]

"Stepping up" asthma treatment

Patients who do not have adequate symptom control after an eight-week trial with a standard ICS dose may require a longer period to determine if they will respond to ICS treatment or they may be switched to an ICS/LABA combination inhaler.[3] The ICS

The START study

The Steroid Treatment As Regular Therapy (START) study assigned 7,138 patients aged 4 – 66 years with mild asthma, diagnosed in the past two years, to either once daily budesonide 400 micrograms or placebo. Post-hoc analysis of the START trial found that budesonide halved the risk of asthma-related adverse events, decreased lung function decline and improved symptom control across all groups of patients.[6] This included patients with symptoms occurring zero to one times per week.[6] The rate of adverse events of patients taking budesonide in START was similar to those taking placebo.[7] These results suggest that many patients with asthma will benefit from earlier initiation of ICS treatment than is recommended by many guidelines.

Table 1: Recommended clinically equivalent standard daily doses of ICS for adults with asthma[8, 9]

Type of ICS and standard starting dose	Dose per inhalation (micrograms)	Patients should take	Subsidised brand and inhaler type
Beclomethasone dipropionate 400 – 500 micrograms/day	50	Four inhalations, twice daily	Beclazone metered dose inhaler (MDI)
	100	Two inhalations, twice daily	
	250	One inhalation, twice daily	
Beclomethasone dipropionate extrafine 200 micrograms/day*	50	Two inhalations, twice daily	Qvar MDI
	100	One inhalation, twice daily	
Budesonide 400 micrograms/day	100	Two inhalations, twice daily	Pulmicort dry powder inhaler (DPI)
	200	One inhalation, twice daily	
	400	One inhalation, once daily	
Fluticasone propionate 200 – 250 micrograms/day	50	Two inhalations, twice daily	Flixotide DPI, Flixotide and Floair MDIs
	100	One inhalation, twice daily	Flixotide DPI
	125	One inhalation, twice daily	Flixotide and Floair MDIs

* Aerosol droplets are on average approximately ten times smaller than droplets in beclomethasone dipropionate

component of combination treatment may be increased once the patient's response to an ICS/LABA has been assessed.

Information on initiating LABA treatment is available in the article "Adding a LABA to asthma treatment for adults"

Managing any adverse effects of ICS treatment

Treatment with an ICS can cause local or systemic adverse effects. At standard doses the risk of clinically significant adverse effects is relatively low, although the risk is increased in patients who are also taking potent topical corticosteroids.[5] At standard doses dysphonia and oral candidiasis are the most common adverse effects of ICS treatment.[5] Oral rinsing after taking an ICS reduces the risk of ICS-related adverse effects.[2] It is advisable to check the inhaler technique of any patient who may be experiencing adverse effects. Poor inhaler technique is associated with an increased risk of: poor asthma control, hospitalisation, courses of oral steroids and use of antibiotics.[10] Errors that are frequently seen in patients using inhalers include not holding their breath after an inhalation, inhaling too early, not exhaling before actuation and not shaking the inhaler.[10]

The extent of systemic ICS absorption is dependent on the inhaler device, particle size, deposition and the individual properties of the active ingredient.[11] Anxiety, depression, sleep disturbances, behavioural changes, e.g. hyperactivity and irritability, hyperglycaemia, skin thinning and bruising have been reported in patients taking inhaled corticosteroids.[12] There may also be a small increased risk of glaucoma in some patients.[12] Hypersensitivity reactions, e.g. rash and angioedema, to ICS treatment are uncommon and paradoxical bronchospasm is a very rare adverse event.[12] A reduction in bone mineral density following long-term ICS use at high doses may increase the risk of osteoporosis in some patients.[12] There is no clear guidance on when to consider a bisphosphonate for a patient taking long-term high-dose ICS,[13] however, this decision can be guided by a risk assessment including the patient's age, history and results of dual-energy X-ray absorptiometry (DEXA).

"Stepping down" the ICS regimen

The risk of ICS-related adverse effects can be decreased by reducing the dose. This may be appropriate for patients with asthma symptoms that have been well-controlled for three months who have a low exacerbation risk.[3] A 50% ICS dose reduction can be trialled, regardless of the patient's starting dose and dose tapering is not required. This can be achieved by either:

- Halving the number of inhalations, e.g. beclomethasone dipropionate, 100 micrograms TWO inhalations twice daily is reduced to ONE inhalation, twice daily; or
- Taking an ICS only in the evening, e.g. budesonide* 400 micrograms, daily (two inhalations of a 100 microgram inhaler, twice daily) becomes budesonide 200 micrograms, daily (two inhalations of a 100 microgram inhaler, in the evening).

* Budesonide is the only ICS subsidised in New Zealand that is licensed for once-daily dosing.[12]

Complete withdrawal of ICS treatment is not recommended,[3] as this is likely to result in an exacerbation. However, a temporary withdrawal may be appropriate for patients with seasonal symptoms with treatment resuming at the first onset of symptoms.

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References

1. Barnes P. Diseases of the respiratory system. In: Harrison's principles of internal medicine. McGraw-Hill 2015. 1669–80.
2. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2017. Available from: http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention (Accessed Apr, 2017).
3. Beasley R, Hancox RJ, Harwood M, et al. Asthma and Respiratory Foundation NZ adult asthma guidelines: a quick reference guide. N Z Med J 2016;129:83–102.
4. Bårnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. Respir Care 2015;60:455–68. doi:10.4187/respcare.03200
5. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma: A national clinical guideline. 2016. Available from: www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2016 (Accessed Apr, 2017).
6. Reddel HK, Busse WW, Pedersen S, et al. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet Lond Engl 2017;389:157–66. doi:10.1016/S0140-6736(16)31399-X
7. Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet Lond Engl 2003;361:1071–6. doi:10.1016/S0140-6736(03)12891-7
8. Holt S, Suder A, Weatherall M, et al. Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. BMJ 2001;323:253–6.
9. Masoli M, Holt S, Weatherall M, et al. Dose-response relationship of inhaled budesonide in adult asthma: a meta-analysis. Eur Respir J 2004;23:552–8.
10. Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med 2011;105:930–8. doi:10.1016/j.rmed.2011.01.005
11. Tattersfield AE, Harrison TW, Hubbard RB, et al. Safety of inhaled corticosteroids. Proc Am Thorac Soc 2004;1:171–5. doi:10.1513/pats.200402-016MS
12. New Zealand Formulary (NZF). NZF v57. 2017. Available from: www.nzf.org.nz (Accessed Mar, 2017).
13. Chee C, Sellahewa L, Pappachan JM. Inhaled corticosteroids and bone health. Open Respir Med J 2014;8:85–92. doi:10.2174/1874306401408010085