POSITION STATEMENT

The role of corticosteroids in the management of childhood asthma

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ABSTRACT

Preventive treatment

- Inhaled corticosteroids are indicated in children with asthma who have more than mild persistent asthma or are unresponsive to non-steroidal medications after 2–4 weeks.
- Initial administration of 400 μg/day of chlorofluorocarbon-beclomethasone dipropionate, or budesonide, or 200 μg/day of fluticasone propionate or hydrofluoroalkane-beclomethasone dipropionate, is suggested, with subsequent titration of the dose to achieve ongoing control with the lowest dose possible.
- In situations where asthma control cannot be achieved with the above doses of inhaled corticosteroids, the addition of a long-acting β_2-agonist, theophylline or a leukotriene antagonist should be considered.
- Specialist referral is recommended in children requiring high doses of inhaled steroids, regular oral steroids or in whom there is concern about possible steroid side effects.

Treatment of acute asthma

- Systemic corticosteroid therapy is recommended for children with moderate to severe acute asthma or if there is incomplete response to β_2-agonists.
- Initial administration of 1 mg/kg prednisolone (maximum, 50 mg) orally is suggested, and this may be repeated every 12–24 hours, depending on response. While a course of up to three days is generally sufficient, in more severe cases a prolonged course (with tapering) may occasionally be indicated.
- The need for recurrent systemic corticosteroid therapy for acute episodes is an indication for reassessment of the child's interval therapy.

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TEN YEARS AGO, the position statement of the Thoracic Society of Australia and New Zealand on the role of corticosteroids in the management of childhood asthma[1] highlighted the concepts of asthma as a disease of airway inflammation, and outlined the evidence for the value of corticosteroids in both acute and preventive management. Since then, these concepts have been refined, new medications have become available and information on the efficacy and safety of corticosteroids in childhood asthma has been consolidated. This position statement updates the recommendations for the role of corticosteroids in childhood asthma.

Preventive treatment

The National Asthma Council's *Asthma management handbook*[2] recommends that preventive therapy should be commenced when:

- the patient requires a β_2-agonist more than 3–4 times a week;
- there are symptoms more than 3–4 times per week between attacks;
- asthma significantly interferes with physical activity despite appropriate pretreatment;
- attacks occur more than every 6–8 weeks;
- attacks are infrequent but severe or life threatening; or
- spirometry shows reversible airflow obstruction between attacks.

In children, non-steroidal medications such as sodium cromoglycate or nedocromil sodium (in children aged over two years) are recommended as first-line preventive therapy for frequent episodic asthma (attacks less than six weeks apart). Inhaled corticosteroids are recommended at presentation for children with more severe persistent asthma or those who are unresponsive to non-steroidal anti-inflammatory therapy.[2]

Some controversy remains as to whether inhaled corticosteroids should be used more aggressively in children with asthma,[3] with conflicting evidence from studies with significant design flaws[4,5] [E3]. A recent randomised-controlled trial compared the relative benefits of β_2-agonists alone (placebo group), nedocromil sodium (8 mg twice daily) and budesonide (200 μg twice daily), given for 4–6 years, on long term outcome in 1041 children with mild to moderate persistent asthma (Childhood Asthma Management Program [CAMP] study)[6] [E2]. There was no significant difference between either treatment and placebo in the primary outcome, namely the change from baseline in forced expiratory volume in one second after the administration of bronchodilator. Thus, this study does not support the suggestion that delay in commencing inhaled steroid therapy is associated with a reduction in lung function.

Inhaled corticosteroids

Efficacy: A recent systematic review of randomised trials examining the effectiveness of prophylactic inhaled steroids in childhood asthma concluded that they were effective, compared with placebo, in improving both clinical (symptom scores or β_2-agonist use) and laboratory (peak expiratory flow) outcomes[7] [E1]. Although there appeared to be considerable heterogeneity in the population included in the analysis, most children had persistent symptoms. There was also a trend for inhaled steroids to be more effective in reducing symptoms in older children, in those with more severe disease, and at higher doses. In contrast, a Cochrane review examining the role of inhaled steroids for episodic viral wheeze concluded that there was no demonstrable reduction in hospitalisation, oral corticosteroid use or frequency and duration of the acute episode[8] [E1].

The CAMP study[6] provides the best comparison of the relative efficacy of non-steroidal and steroidal preventive medication. It showed that asthma control, in terms of symptoms, β_2-agonist and prednisone use and morbidity, was best with the use of budesonide, which also significantly improved airway responsiveness to methacholine. However, nedocromil also reduced urgent care visits and prednisone use compared with placebo. A recent systematic review of inhaled sodium cromoglycate concluded that there was insufficient evidence to support its role as first-line preventive treatment in childhood asthma[9] [E1]. However, that review acknowledged the variable methodological quality of the studies. In contrast, a large multicentre, randomised-controlled study of children and adults with persistent asthma (not included in the systematic review) showed improved control with sodium cromoglycate[10] [E2].

Thus, while the threshold for using inhaled steroids may have lowered, we believe that, based on current evidence, non-steroidal medications should still be considered first-line preventive treatment for children with frequent episodic or mild persistent asthma [E4]. This recommendation is based on the lack of evidence of efficacy of inhaled steroids in children with viral wheeze[8] and the conflicting evidence on the efficacy of sodium cromoglycate.[9,10] However, lack of evidence of efficacy does not equate with proof of no efficacy, and further studies are required to investigate the relative value of inhaled steroids and non-steroidal medications, including leukotriene antagonists,[11,12] in these patients.

Dosage: A dose–response study of budesonide in children with moderate to severe asthma indicated that exercise-induced asthma is controlled in 83% with a dose of 400 μg per day[13] [E2]. Therefore, an initial dose of 400 μg of beclomethasone dipropionate or budesonide or 200 μg of fluticasone propionate should be adequate in most children. The comparative efficacy of the lower doses of fluticasone with higher doses of beclomethasone and budesonide has been established for both adults and children[14] [E1]. With the change from chlorofluorocarbon (CFC) to hydrofluoroalkane (HFA) propellants for metered-dose inhalers, beclomethasone is delivered in more than twice the quantity to the lung.[15] Preliminary experience in a six-month open-label study suggests that HFA-beclomethasone provides comparable efficacy and safety at half the dose when compared with CFC-beclomethasone[16] [E2]. While considerable further clinical experience is still required, it appears that a reasonable starting dose for HFA-beclomethasone would be 200 μg, similar to fluticasone.

After commencement of therapy, the dose of inhaled corticosteroid should be titrated according to clinical response, aiming for the minimum dose that will provide continuing control of asthma symptoms. While most studies of inhaled corticosteroids in children have employed twice-daily dosing, recent evidence suggests that once-daily dosing is also effective, particularly in children with less severe asthma[17] [E2]. The dose of inhaled corticosteroid delivered to the lungs will depend on many factors, including the delivery device, the age of the child, and individual variation in inhaler technique and adherence. While it is difficult to be dogmatic about what dose is likely to be effective, dose titration should take into account variations in dose delivery. A further factor that may need to be considered in situations where control is not achieved, despite escalating doses, is whether the diagnosis of asthma is correct. In these instances cessation of treatment rather than further dose escalation may be the best option.

Side effects

Topical effects: Although both dysphonia and oral candidiasis have long been recognised as complications of inhaled steroid use,[18] recent systematic reviews of inhaled steroid therapy for childhood asthma indicated that these are uncommon problems in children[7,19] [E1].

Systemic effects: A recent systematic review of systemic adverse effects of inhaled corticosteroid therapy in healthy volunteers and both children and adults with asthma concluded that "Marked adrenal suppression occurs with high doses of inhaled corticosteroid above 1500 μg per day (750 μg/day for fluticasone propionate), although there is a considerable degree of interindividual susceptibility"[20] [E1]. Meta-analysis showed a significantly steeper dose-related adrenal suppression slope with fluticasone compared with beclomethasone or budesonide[20] [E1], even allowing for its greater potency. In contrast, a meta-analysis of systemic activity of fluticasone at half the microgram dose compared with beclomethasone and budesonide in both children and adults with asthma concluded that there was no greater adrenal suppression with fluticasone[14] [E1], even at high doses. These opposing conclusions may be the result of differences in patient groups (normal patients or those with asthma), interindividual susceptibility, and methods for assessing adrenal suppression.

Dose-dependent, short-term suppression of lower leg length growth (measured by knemometry) has been shown for both beclomethasone and budesonide[21] [E2]. Knemometry results with fluticasone have been variable[22,23] [E2]. In one study systemic activity, as assessed by knemometry, was greater with budesonide, while cortisol suppression was greater with fluticasone, further highlighting the difficulties

in comparing measures of systemic activity of inhaled corticosteroids. It is also important to emphasise that, while knemometry appears to be a useful measure of systemic activity, it is not predictive of long term statural growth,[24] but rather appears to reflect short-term suppressive effects on collagen turnover.[25]

The potential for inhaled corticosteroids to suppress short-term linear growth in children has been well demonstrated[4,6,20,21,24,26,27] [E1, E2, E3]. Although a systematic review found these effects were seen mainly in children with mild asthma, where doses of 400 μg per day were shown to affect growth over 7–12 months[27] [E1], there is one study suggesting effects with beclomethasone even in children with more severe asthma[28] [E2]. The recently published CAMP study showed that this growth reduction was seen mainly in the first year of treatment[6] [E2], and current evidence indicates no long-term effect of inhaled corticosteroids on eventual adult height[20,21,24,26,29] [E1, E2, E3]. In view of differing patient susceptibility, we believe it is still prudent to monitor growth in children with asthma who are taking inhaled corticosteroids, also allowing for the potential for delay in the pubertal growth spurt in these children.[30]

Evaluation of potential effects of inhaled corticosteroids on bone density is in its infancy. To date, studies in children have generally been reassuring, with no evidence of abnormal bone mineral density with long-term inhaled corticosteroid treatment [20,24,28,31,32] [E1, E2, E3]. Nevertheless, one recent Australian study has suggested a dose-dependent short term effect on bone accretion in prepubescent children[33] [E3]. Other systemic complications, such as posterior subcapsular cataracts and skin bruising, appear rare in children[19] [E3].

In conclusion, there is clear evidence of a dose-related systemic effect of inhaled corticosteroids as measured by adrenal suppression [E1] and knemometry [E2]. While it remains difficult to be certain of the clinical significance of this effect, it is clear that other factors, such as individual susceptibility, severity of asthma, age of the child, pubertal status and dose delivery, may potentially increase the risk of systemic toxicity. While studies of long-term systemic effects in children are generally reassuring [E1], we need to remain vigilant to the possibility of these effects in individual patients.

Minimising side effects: It is important to ensure that inhaled corticosteroids are used appropriately in children with asthma. The fact that effects on growth have been seen mainly in children with mild asthma[27] [E1] supports our recommendation for using non-steroidal preventive medication as first-line preventive treatment for children with frequent episodic or mild persistent asthma [E4]. In addition, children who have episodic cough without wheeze are unlikely to benefit from inhaled corticosteroids[34] [E2]. Even in children with persistent asthma who require inhaled corticosteroid prophylaxis, it is important to ensure maintenance of control with the minimum dose by back-titration when symptomatic control is achieved for at least three months to reduce the potential for side effects.

Although methods for reducing oropharyngeal deposition, such as spacer devices and mouth rinsing, will reduce the likelihood of topical side effects, particularly candidiasis, it is clear that pulmonary absorption is the major contributor to systemic activity (especially with the newer inhaled steroids such as budesonide and fluticasone).[35] Thus, any improvement in drug delivery to the lung is likely to be associated with an increase in systemic activity. However, this should be offset by the lower dose required to achieve efficacy.

The other important change in the use of inhaled corticosteroids in the management of asthma is recognition of an upper dose limit of inhaled corticosteroids above which there is little increase in efficacy, but significant increases in systemic activity. This flat dose–response curve is clearly demonstrated in studies on adults with asthma which compared the addition of a long-acting β_2-agonist with doubling the dose of inhaled corticosteroid — all studies showed better control with the addition of the β_2-agonist[36-38] [E2]. While similar benefits were not shown in the only paediatric study examining this issue[39] [E2], this almost certainly reflected the fact that asthma control was achievable with low-dose inhaled corticosteroids alone. While further studies in children are required, we believe that, extrapolating from data in adults, the addition of long-acting β_2-agonists should be considered in children with asthma who have persistent symptoms (particularly nocturnal) despite 400 μg per day of beclomethasone or budesonide, or 200 μg per day of fluticasone or HFA-beclomethasone [E4]. However, if no clinical benefit can be demonstrated after 4–6 weeks, β_2-agonist therapy should be discontinued. Other medications which may have a "steroid sparing" benefit in this situation include low-dose theophylline, which has been shown to be as effective as doubling inhaled corticosteroid dose in adults[40] [E2], and the new leukotriene antagonists, for which data are limited and suggest only modest additional benefit[41] [E2].

Systemic corticosteroids

Most children with asthma requiring preventive treatment can be managed with regular inhaled corticosteroids with or without a long-acting β_2-agonist. A short course of oral corticosteroid may be helpful in obtaining rapid control during stabilisation and carries little risk of additional systemic toxicity. The therapeutic limit (flat part of the dose–response curve) of inhaled corticosteroid is currently believed to be around 1000 μg per day of beclomethasone or budesonide and 500 μg per day of fluticasone. There are insufficient data available to define a limit for HFA-beclomethasone, although it is likely to be similar to fluticasone. Once these limits are reached, it is important to consider issues such as correct diagnosis, adherence, inhaler technique and psychosocial issues, as well as other pharmacological options. While it may be necessary to consider the use of regular systemic corticosteroids as one of these options, this is an absolute indication for specialist referral.

1: Recommendations for the use of corticosteroids in the preventive treatment of childhood asthma

- Non-steroid preventive medications are recommended as first-line treatment in children with frequent episodic or mild persistent asthma (E4).
- Inhaled corticosteroids are indicated in children who have more than mild persistent asthma, or are unresponsive to non-steroid medications after 2 – 4 weeks (E1).
- The dose of inhaled corticosteroid needs to be titrated against the severity of the disease (as assessed by clinical symptoms and pulmonary function tests where applicable) and the lowest dose to achieve and maintain control should be used. An initial dose of 400 μg/day of chlorofluorocarbon-beclomethasone dipropionate (CFC-BDP) or budesonide (BUD), or 200 μg/day of fluticasone propionate (FP) or hydrofluoroalkane-beclomethasone dipropionate (HFA-BDP), will achieve control in the majority of children (E2).
- The need for high doses of inhaled corticosteroids (500 μg/day CFC-BDP or BUD or 250 μg/day FP or HFA-BDP in children aged under five years, or 1000 μg/day CFC-BDP or BUD or 500 μg/day FP or HFA-BDP in those aged over five years) is an indication for specialist assessment (E4).
- Dose-dependent systemic activity has been demonstrated for inhaled corticosteroids, although significant clinical side effects are unusual (E1). Short term linear growth suppression has been demonstrated in children, but no long term effects on growth or bone density have been reported to date (E1). Nevertheless, monitoring of growth is recommended in children taking inhaled corticosteroids (E4).
- Manoeuvres to decrease oropharyngeal deposition (spacers, mouth rinsing) will reduce the risks of topical side effects, but will not significantly decrease, and may increase, systemic activity, particularly with the newer inhaled corticosteroids, where pulmonary absorption is the main contributor to systemic effect (E3).
- In situations where effective control of asthma cannot be achieved with doses of 400 μg/day CFC-BDP or BUD, or 200 μg/day FP or HFA-BDP, the addition of a long acting β_2-agonist, theophylline or a leukotriene antagonist should be considered (E4 – extrapolated from E1 adult data for long-acting β_2-agonists and theophylline).
- Occasionally, long-term systemic corticosteroids may be needed in children with severe persistent asthma which remains poorly controlled despite high doses of inhaled corticosteroids. Specialist referral is strongly recommended before commencing such therapy (E4).

Treatment of acute asthma

Systemic corticosteroids

Efficacy: Early use of systemic corticosteroid therapy in acute exacerbations of asthma in adults and children reduces hospital admissions and also prevents relapse among outpatients[42,43] [E1].

Indications: Systemic corticosteroid therapy should be considered in children with acute episodes of asthma whose response to treatment with a β_2-agonist is poor (less than four hours' relief) or those who require frequent treatment with a β_2-agonist (every four hours) for 36–48 hours. In general, this means that any child with moderate to severe acute asthma based on National Asthma Campaign criteria[2] should receive systemic steroids [E4].

Dosage: Although there is no consensus about dose or duration of therapy[42] [E1], low doses of corticosteroids appear to be as effective as high-dose regimens[44] [E1]. Our current recommendation in children is a dose of oral prednisolone of 1 mg per kg (maximum 50 mg) given initially and repeated every 12–24 hours, depending on clinical progress. Duration of therapy will generally be up to three days, but, in children with severe persistent asthma, a more prolonged course may occasionally be needed, with tapering of the dose to prevent relapse. Although a recent comparison of oral dexamethasone (0.6 mg/kg) with oral prednisololone (2 mg/kg) showed that a shorter course of dexamethasone provided equal benefit and was better tolerated[45] [E2], concerns were raised about the greater potential for adrenal suppression with dexamethasone relating to its longer half-life.[46] While there appears to be no definite advantage of parenteral over oral corticosteroids[42,43] [E1], intravenous corticosteroids (1 mg/kg methylprednisolone or 5 mg/kg hydrocortisone) will be needed if the child cannot tolerate oral medication or is extremely ill or unconscious.

Side effects: The side effects of systemic corticosteroids are well documented,[47] and risks are related to dose and duration of use. Using hypothalamic–pituitary–adrenal-axis suppression as an index of systemic toxicity, systemic corticosteroid bursts of up to two weeks[48,49] [E2] do not reduce adrenal response. However, 20% of children who have four or more bursts a year show suboptimal adrenal response[49] [E3]. Other, rare problems with systemic steroid therapy include acute steroid-induced myopathy[50,51] and anaphylaxis after intravenous hydrocortisone administration.[52,53]

Inhaled corticosteroids

High doses of inhaled corticosteroids (1600–2250 μg/day) provide a partially effective strategy for treating episodes of

2: Recommendations for the use of corticosteroids in the treatment of acute severe asthma in children

- Systemic corticosteroid therapy is recommended for children with moderate to severe acute asthma or if there is incomplete response to β_2-agonists (E1).
- An initial dose of 1 mg/kg prednisolone (maximum 50 mg) orally is recommended and this may be repeated every 12–24 hours, depending on response. While a three-day course is generally sufficient, in severe cases a more prolonged course with tapering may be indicated (E4).
- Intravenous corticosteroids may be indicated if oral therapy is poorly tolerated or the child is critically ill (E1).
- While oral corticosteroid therapy of less than two weeks' duration carries little risk of long term HPA-axis suppression, frequent courses (four or more per year) may carry a cumulative risk (E2).
- The need for recurrent systemic corticosteroid therapy requires reassessment of the child's interval therapy (particularly in those with persistent asthma) (E4).
- While high dose inhaled corticosteroids are effective in acute asthma (E1), oral corticosteroids remain the treatment of choice because of ease of administration, cost, and greater efficacy in severe acute asthma (E2).

Background and evidence base of recommendations

This position statement was formulated by the authors at the request of the Education and Research Subcommittee of the Thoracic Society of Australia and New Zealand (TSANZ). It was then submitted to the Subcommittee for consideration and underwent independent external review. It was also circulated to all members of the Australasian Paediatric Respiratory Group for information and comment. The position statement was then revised in line with the feedback from these sources, before being resubmitted for final consideration by the Education and Research Subcommittee and its endorsement by the TSANZ.

The recommendations are based on the following levels of evidence, simplified from the NHMRC's "Quality of evidence ratings":[57]

E1 Level 1: Systematic review or meta-analysis of all relevant randomised-controlled trials (RCTs).

E2 Level 2: Well-designed RCTs.

E3 Level 3: Well-designed cohort or case–control studies.

E4 Level 4: Consensus opinion of authors.

viral-induced wheeze, with some reduction of oral corticosteroid requirements[8] [E1]. Although high doses of inhaled corticosteroids have been shown to be as effective as oral prednisolone[54] [E2], oral prednisolone provided a much better clinical outcome in children with severe acute asthma[55] [E2]. The only paediatric study to have investigated doubling the dose of inhaled corticosteroids during an acute exacerbation (often incorporated into asthma action plans) failed to show any benefit[56] [E2]. In conclusion, while there is some evidence supporting the use of high doses of inhaled corticosteroids in treating acute asthma [E1], short-course oral corticosteroids remain the preferred option because of ease of administration, relative cost and their greater efficacy in severe acute asthma [E2].

Conclusions

There is Level 1 evidence supporting the efficacy and safety of inhaled corticosteroid therapy in preventive treatment of childhood asthma. This assumes that appropriate patients are targeted and the dose is titrated against clinical benefit and risk of side effects. The recommendations for the use of inhaled corticosteroids in preventive treatment of childhood asthma appear in Box 1. There is also Level 1 evidence supporting the efficacy of systemic corticosteroids in the treatment of acute asthma in children and our recommendations are summarised in Box 2.

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