



The Thoracic Society of Australia and New Zealand

The Role of Corticosteroids in the Management of Childhood Asthma.

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This document will be reviewed in 2015 or earlier if significant developments occur.



Conflicts of Interest Declaration

Prof Peter van Asperen is currently a member of the MSD (Aust) Paediatric Respiratory Physician Advisory Board and has received speaker fees from MSD (Aust) for presentations on management of asthma and wheeze in children. He is also a member the GSK Paediatric Respiratory Taskforce which has been convened to ensure appropriate prescribing of Seretide in children. His Department has also received research funding in the past from GSK, Astra Zeneca, MSD, Boehringer Ingelheim & Altana for involvement in clinical trials but is not currently receiving funding from these companies.

Prof Craig Mellis is currently a member of the MSD (Aust) Paediatric Respiratory Physician Advisory Board and has received speaker fees from MSD (Aust) for presentations on management of asthma and wheeze in children. He is also a member the GSK Paediatric Respiratory Taskforce which has been convened to ensure appropriate prescribing of Seretide in children. He has also received payment from “UpToDate” (Electronic Textbook) for review of topics/chapters.

Prof Peter Sly has no current conflicts of interest to declare.

Prof Colin Robertson is currently a member of the MSD (Aust) Paediatric Respiratory Physician Advisory Board and has received speaker fees from MSD (Aust) for presentations on management of asthma and wheeze in children. He is also a member the GSK Paediatric Respiratory Taskforce which has been convened to ensure appropriate prescribing of Seretide in children.

ABSTRACT

Preventive treatment

- Inhaled corticosteroids (ICS) are indicated as first line preventer treatment in children with moderate to severe persistent asthma or as an alternative to non steroidal preventers in those with frequent intermittent or mild persistent asthma. Based on current evidence, it is preferable to trial non steroidal preventers first in children with frequent intermittent or mild persistent asthma and proceed to ICS if there is an inadequate response after 2-4 weeks.
- An initial dose of 400mcg/day of budesonide (BUD) or 200mcg/day of fluticasone propionate (FP) or hydrofluoroalkane-beclomethasone dipropionate (HFA-BDP) or 160 mcg/day of ciclesonide (CIC) is suggested with the dose back titrated to achieve ongoing control with the lowest dose possible.
- In situations where asthma control cannot be achieved with 400mcg/day of CFC- BUD or 200mcg/day of FP or HFA-BDP or 160 mcg/day of CIC, the main step up options include increasing the inhaled steroid dose or the addition of a long-acting beta-agonist (LABA) or a leukotriene antagonist.. In the absence of evidence of safety and efficacy, the use of LABAs is not recommended in children aged 5 years or younger. The addition of leukotriene antagonists may be particularly effective in those children with ongoing exercise induced symptoms, despite regular inhaled corticosteroids.
- ICS must be used with an age-appropriate delivery device and inhaler technique should be checked before considering treatment changes.



- Manoeuvres to decrease oro-pharyngeal deposition (spacers, mouth-rinsing) will reduce the risk of topical side effects but will not decrease (and may increase) the risk of systemic activity as this relates primarily to pulmonary deposition. However this will also result in improved efficacy which is likely to allow a reduction in inhaled steroid dose.
- Specialist referral is recommended in children requiring high dose inhaled steroids: If 5 years of age or younger; > 400mcg/day BUD or 200-250mcg/day FP or HFA-BDP. If over 5 years of age; > 800mcg/day BUD or 400 - 500mcg/day FP or HFA-BDP or 320mcg CIC); or regular oral steroids, or where there is concern about possible steroid side effects.

Treatment of Acute Asthma

- In general a short course of systemic corticosteroid therapy is recommended for children assessed as having a moderate to severe acute asthma exacerbation, or if there is an incomplete response to beta-agonists.
- The use of systemic corticosteroids in pre-school children, particularly those with intermittent viral induced wheezing, should be limited to those with wheeze severe enough to need admission to hospital.
- An initial dose of 2mg/kg prednisolone (maximum 60 mg) orally is recommended and subsequently daily doses of 1mg/kg if required. While a 3 day course is generally sufficient, in severe cases a more prolonged course may be indicated.



- While there is some evidence for the benefit of intermittent high dose inhaled corticosteroids and leukotriene receptor antagonists in an acute exacerbation of asthma, oral corticosteroids remain the treatment of choice.

- The need for recurrent systemic corticosteroid therapy for acute episodes is an indication for reassessment of the child's interval therapy and specialist referral.



INTRODUCTION

In 1992 the original position statement of the Thoracic Society of Australia and New Zealand on the role of corticosteroids in the management of childhood asthma was published (1). Eight years ago, a revised version incorporated the current evidence for the value of corticosteroids in both acute and preventive management of asthma in children (2). The last 8 years have seen further developments in our understanding of asthma in children with the recognition of different wheezing phenotypes in the preschool years (3,4) and the need for separate asthma management guidelines in children 5 years and younger (3,4). In addition, we have considerably more clinical research evidence on the role of newer agents, such as the leukotriene receptor antagonist, montelukast, and the combination products, (ie, fluticasone propionate & salmeterol xinafoate; budesonide & eformoterol fumarate), although studies on combination therapy in children are limited to those 4 years of age and older. This information has enabled more appropriate positioning of these medications in the management of children with different patterns of asthma, and in different age groups. This current position statement therefore updates the recommendations for the role of corticosteroids (as well as the roles of leukotriene receptor antagonists and combination medications) in paediatric asthma management, by incorporating recent evidence based information and also highlights the different management approaches in pre-school children.



PREVENTIVE TREATMENT

Principles of drug treatment in children and adolescents

The National Asthma Council (NAC) Asthma Management Handbook (5) provides a comprehensive overview of the role of preventive treatment in childhood asthma. A stepwise approach to drug therapy is advocated with treatment commencing at the step most appropriate to the level of asthma severity.

**Table 1. Classification of interval severity of asthma in children
(Modified from NAC Asthma Management Handbook 2006 [5] with permission)**

	Daytime symptoms between exacerbations	Night-time symptoms between exacerbations	Exacerbations	PEF or FEV₁[*]	PEF variability^{**}
Infrequent intermittent	Nil	Nil	Brief, Mild Occur < every 4–6 weeks	> 80% predicted	< 20%
Frequent intermittent	Nil	Nil	Occur > every 4-6 weeks	At least 80% predicted	< 20%
Mild persistent	> once per week but not every day	> twice per month but not every week	May affect activity and sleep	At least 80% predicted	20–30%
Moderate persistent	Daily	> once per week	At least twice per week Restricts activity or affects sleep	60–80% predicted	> 30%
Severe persistent	Continual	Frequent	Frequent Restricts activity	≤ 60% predicted	> 30%

An individual's asthma category (infrequent intermittent, frequent intermittent, mild persistent, moderate persistent or severe persistent) is determined by the level in the table that corresponds to the **most severe** feature present. Other features associated with that category need not be present.

FEV₁: Forced expiratory volume in 1 second; PEF: peak expiratory flow.
(in children old enough to perform reliable lung function)

* Predicted values are based on age, sex and height

** Difference between morning and evening values



Most children (75%) have a pattern of infrequent intermittent asthma (episodes less than every 4-6 weeks) and do not require any long term preventive therapy. Children with frequent intermittent or mild persistent asthma (symptoms more than once a week but not every day) should receive either a non steroidal preventer (oral montelukast or an inhaled cromone) or low dose inhaled corticosteroids. The relative benefits of these treatment options in these children will be discussed in detail below. For children with moderate to severe persistent asthma, an inhaled corticosteroid is the preferred option. Since there is limited evidence on both the efficacy and safety of combination therapy in children, they should **not** be used as first line preventer therapy in children and can not be recommended for use in children aged 5 years or younger. A summary of currently available evidence will be presented in detail below. If control is not achieved on the initial preventer therapy, it is important to review the diagnosis of asthma. This is particularly important in pre-school children since many children with recurrent cough are mislabeled as having asthma (6), and different wheezing phenotypes will require different treatment approaches (3,4). In addition to questioning the diagnosis of asthma, it is essential to check the child's inhaler technique, and their adherence with treatment, before escalating the level of preventer therapy. Step down treatment ('back-titration') is advocated once control has been achieved and sustained for at least 3 months.

Non Steroidal Preventers

Inhaled Cromones

A systematic review of inhaled sodium cromoglycate concluded that there is insufficient evidence concerning its efficacy over placebo, and suggested that publication bias is likely to have overestimated the beneficial effects of sodium



cromoglycate as maintenance therapy in childhood asthma (7). However, this conclusion has been challenged by a more recent analysis of the data, which demonstrated a beneficial effect, particular in older children (8). A systematic review of inhaled corticosteroids versus sodium cromoglycate concluded that inhaled corticosteroids were superior on measures of both asthma control and lung function in children and adults, thus supporting the use of inhaled corticosteroids over sodium cromoglycate in children with persistent asthma (9). A systematic review assessing the effectiveness of nedocromil sodium for persistent asthma in children concluded that while there was some evidence of benefit, further studies were required to establish its relative effectiveness to inhaled corticosteroids (10). Unfortunately, there are major practical difficulties with the cromolyns, due to their tendency for the powder to block the inhaler actuator, and the need for frequent administration (three to four times daily), resulting in a progressive reduction in their role in childhood asthma.

Leukotriene Receptor Antagonists

Two placebo controlled studies of once daily montelukast (4mg in 2-5 year olds and 5mg in 6-14 year olds) in children with persistent asthma have established the efficacy and safety of this medication and form the basis of its current PBS listing for children with frequent intermittent or mild persistent asthma (11,12). A recent systematic review comparing leukotriene antagonists to inhaled corticosteroids in the management of intermittent and / or persistent asthma in adults and children concluded that inhaled corticosteroids should remain first line monotherapy for persistent asthma (13). However, a 12 month randomised trial comparing montelukast with fluticasone (100 mcg/day) in 994 children (aged 6-14 years) with mild persistent asthma, found montelukast was 'non inferior' in terms of the percentage of 'rescue free days' (use of



prn short acting beta-agonists, systemic steroids or other asthma rescue medications).

Children on fluticasone, however, had greater benefits in lung function measurements, quality of life improvement, and reduced risk of asthma exacerbations requiring systemic corticosteroids (14).

Compared to placebo, regular montelukast has been shown to produce a modest reduction in exacerbation risk and corticosteroid courses (either oral or inhaled) in 2-5 year old children with intermittent viral induced wheezing (15). Montelukast has also been shown to reduce the risk of asthma exacerbations in 2-14 year old children related to the Northern Hemisphere September epidemic (due to increased viral exacerbations when children return to pre-school or school after the summer holidays), and this benefit was independent of whether they were on maintenance inhaled corticosteroids (16). This is in contrast to trials showing inhaled corticosteroids are not effective in reducing exacerbation frequency or severity in children with intermittent viral induced wheezing (17). Short-course montelukast given for at least 7 days at the time of asthma exacerbation in children with intermittent asthma has also been shown to provide modest benefit in reducing the severity of the exacerbation (18,19), and reducing health care utilization, and in one of these studies, improving quality of life (18). An additional benefit of montelukast is its proven efficacy for protecting against exercise induced bronchoconstriction (20-21). When used as regular treatment it has been shown to be more effective than long-acting beta-agonists for protection against exercise induced bronchoconstriction in both adults (22,23) and children (24-26). Further, in contrast to regular long-acting beta-agonist use, montelukast is not associated with the development of tolerance to either protection against exercise induced bronchoconstriction, nor response to short acting beta agonists (23,25,26).



Of great importance to paediatric prescribing is the impressive safety profile of montelukast. In placebo controlled and open label extension studies adverse events are similar to those observed for placebo or active control/usual care therapies (27). Although concerns have been raised about behaviour-related adverse events with montelukast, these appear rare in children in clinical trial data (28,29). Post marketing surveillance reports have suggested a slight increase in risk of psychiatric disorders apparently associated with use of montelukast in children (30), although concomitant medication and the severity of underlying asthma were potential confounders in establishing a causal link. Nevertheless, it is prudent to mention to parents the potential association of montelukast with behaviour-related adverse events when commencing treatment and to cease therapy if such adverse events become an issue, as this appears to be associated with resolution of the symptoms (30).

An additional practical issue is that, in Australia, montelukast is only available on PBS subsidised prescription as a sole preventer treatment for children aged 2-14 years and as an add on therapy for children 6-14 years on ICS with ongoing activity related asthma. Outside these age ranges and indications patients will need to pay full price or switch to an alternative therapy. There is also currently no preparation available in Australia for children less than 2 years of age.

Inhaled Corticosteroids

Efficacy

The effectiveness of prophylactic inhaled steroids in childhood asthma is well established (31). Although there is considerable heterogeneity in the populations included in the studies, the majority have included children with persistent symptoms. Studies show a trend for inhaled steroids to be more effective in older children, those



with more severe disease, and at higher doses. Cochrane reviews have established the efficacy of beclomethasone dipropionate (32,33), budesonide (34,35) & fluticasone propionate (36,37) in both adults and children. In addition the equivalent benefit of fluticasone propionate when used at half the dose of beclomethasone dipropionate or budesonide has been established (38). This 50% reduction in dosing requirement has also been achieved with hydrofluoroalkane (HFA) beclomethasone dipropionate (39). Although there is a paucity of studies in children, ciclesonide has been demonstrated to be effective at lower doses in both placebo controlled studies (40), and when compared to other inhaled steroids (41) for persistent asthma in both children and adults.

In contrast to persistent asthma, a Cochrane review on the role of regular inhaled steroids for intermittent viral induced wheezing (17) concluded that there was no demonstrable reduction in hospitalisation, oral corticosteroid use, nor frequency and duration of acute episodes. However, to date only two randomised controlled studies have been performed. A recent systematic review of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma (42), concluded that there was evidence of improved symptoms, lung function, and decreased exacerbations, particularly in those with a diagnosis of asthma.

Dosage

A dose response study using budesonide in children with moderate and severe persistent asthma indicated that 83% achieved control of exercise induced asthma with a dose of 400 mcg/day (43). Therefore an initial dose of 400 mcg of budesonide or 200 mcg of fluticasone propionate should be adequate in the majority of children. Comparable initial doses for HFA beclomethasone is 200mcg daily (38, 39), and for ciclesonide, 160mcg once daily (44, 45)



Following 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 the majority of studies of inhaled corticosteroids in children have employed twice daily dosing, studies with ciclesonide have demonstrated that once daily dosing is effective (44,45). The dose of inhaled corticosteroid delivered to the lungs will depend on many factors including the delivery device, the age of the child, individual variation in inhaler technique, and adherence. While it is difficult to be dogmatic about what dose is likely to be effective, the principles of dose titration should account for 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.

It has previously been argued that in order to prevent the development of airway remodeling, inhaled corticosteroids should be used earlier and more extensively in children with asthma. However, there are now 3 long term randomised controlled trials in both school age (46) and pre-school age children (47,48) which have failed to demonstrate any benefit of long term inhaled corticosteroids on lung function outcome or natural history in children with recurrent wheezing/asthma. Thus these studies do not support the suggestion that delay in commencing inhaled steroids is associated with a permanent reduction in lung function, at least in children with intermittent or mild persistent asthma. In addition, these studies do not support the notion that early institution of inhaled steroids will prevent the development of persistent asthma.



Side Effects

Topical Effects

Although both dysphonia and oral candidiasis have been recognised as complications of inhaled steroid use for a long time (49), systematic reviews of inhaled steroid therapy in childhood asthma indicate that these are uncommon problems in children (31,50). Inhaled corticosteroids may have an adverse effect on dental health in children, particularly the powder forms which have a pH<5.5 which is known to dissolve tooth substance (51). Topical effects can be reduced by use of spacer devices (which reduce oro-pharyngeal deposition) as well as rinsing and spitting after use, which is particularly important with powder inhalers.

Systemic Effects

Systemic effects of inhaled corticosteroids have been well documented in children and include adrenal suppression, growth suppression and effects on bone mineralization (51). A systematic review of systemic adverse effects of inhaled corticosteroid therapy in healthy volunteers and both children and adults with asthma (52) concluded that “Marked adrenal suppression occurs with high doses of inhaled corticosteroid above 1500 mcg/day (750 mcg/day for fluticasone propionate), although there is a considerable degree of inter individual susceptibility”. Meta-analysis showed significantly greater potency for dose related adrenal suppression with fluticasone compared with beclomethasone or budesonide (52). In contrast a meta-analysis of systemic activity of fluticasone at half the daily microgram dose compared to beclomethasone and budesonide in both children and adults with asthma and concluded that there was no greater adrenal suppression with fluticasone (53). These opposing conclusions may be due to differences in patient groups (normals or



asthmatics), inter-individual susceptibility, and methods for assessing adrenal suppression. Clinical adrenal suppression has also been documented in children with asthma (54,55) particularly in those treated with inappropriately high doses.

Dose dependent suppression of short-term lower leg length growth has been demonstrated for both beclomethasone and budesonide (56), using knemometry. Knemometry results with fluticasone have been variable (57,58). 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. Ciclesonide did not affect knemometry or adrenal function measurements in doses up to 160mcg/day over a 2 week period (59). While short-term knemometry appears to be a useful measure of systemic activity, it is not predictive of long-term linear growth (60), but rather appears to reflect short term suppressive effects on collagen turnover (61).

The potential for inhaled corticosteroids to transiently suppress linear growth in children, particularly in the first year of treatment, is well documented (46,51,52,56,60,62,63). However, a recent comparative study of budesonide and ciclesonide suggests again that ciclesonide may have less systemic activity, as linear growth over 12 weeks was greater in the ciclesonide group compared to the budesonide treated children (44). Furthermore a long-term safety study has shown no effect on linear growth of ciclesonide up to 160mcg/day over 12 months (64). A systematic review found these effects had been particularly documented in children with mild persistent asthma where doses of 400 mcg/day beclomethasone were shown to effect growth over a 7 – 12 month period (63), and this may relate to poorer growth in children with moderate to severe persistent asthma which improves with inhaled corticosteroid treatment. However, there is one study suggesting adverse effects with



beclomethasone, even in children with more severe asthma (65). The Childhood Asthma Management Program (CAMP) study again demonstrated growth reduction is mainly seen in the first year of treatment (46), although both the CAMP study (46) and the Prevention of Early Asthma in Kids (PEAK) trial (47), which included a 1 year washout period following the 2 year fluticasone treatment period, demonstrated an ongoing deficit in height at the end of the study (4-6years & 3 years respectively). However, current evidence indicates no long term effect of inhaled corticosteroids on final adult height (52,56,60,62,66). In view of differing patient susceptibility, we believe it is still prudent to monitor growth in children with asthma on inhaled corticosteroids, also taking into account the potential for delay in the pubertal growth spurt in children with asthma (67).

To date, the majority of studies of bone density in children have been reassuring, with no evidence of abnormal bone mineral density with long-term treatment with any of the inhaled corticosteroids (51,52,60,65,68,). However one Australian study has suggested a dose dependent short term effect on bone accretion in pre-pubescent subjects (69) and follow up of the patients in the Childhood Asthma Management Program (CAMP) study demonstrated that cumulative inhaled corticosteroid use was associated with a small decrease in bone mineral accretion in boys, but not girls, and no increased risk for osteopenia (70). Another Australian study demonstrated an association between inhaled corticosteroid use and increased fracture risk (71) although a much larger population-based nested case-control study in the UK concluded that exposure to inhaled steroids does not materially increase the fracture risk in children and adolescents compared with non-exposed individuals (72). Other systemic complications, such as posterior subcapsular cataracts and skin bruising, appear rare in children (51).



In conclusion, there is clear evidence of a dose related systemic effect of inhaled corticosteroids as measured by adrenal suppression and knemometry. 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, total dose and dose delivery may increase the risk of systemic toxicity. While studies of long term systemic effects in children are generally reassuring, 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 (63) supports the recommendation for using non-steroid preventive medication as first line preventive treatment for children with frequent intermittent or mild persistent asthma. In addition, children who have episodic cough without wheeze are unlikely to have asthma, and are unlikely to benefit from inhaled corticosteroids (6). Even in children with persistent asthma who require inhaled corticosteroid prophylaxis, it is important to ensure maintenance of control with the minimum dose. Thus, to reduce the potential for side effects ‘back titration’ should be attempted once symptomatic control has been achieved for at least 3 months.

Although methods for reducing oro-pharyngeal deposition such as spacer devices and mouth rinsing will reduce the likelihood of topical side effects, particularly candidiasis, it is clear that the major contributor to systemic activity, especially with budesonide and fluticasone, is via pulmonary absorption (73). 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. Studies using ciclesonide (which is cleaved to its active metabolite in the lung) have



shown lower systemic activity than comparable doses of budesonide (44) and fluticasone (45) and no effect on knemometry (59) or linear growth for up to 12 months (44,64), in doses up to 160mcg/day which may relate to high systemic clearance and protein binding in the blood (59).

An important issue in the use of inhaled corticosteroids is recognition of an upper dose limit of inhaled corticosteroids, above which there is little increase in efficacy, but significant increases in systemic activity (33,35,37,51). This flattening of the dose-response curve in children occurs at doses above 200mcg/day of fluticasone propionate, while above 500mcg/day of fluticasone propionate, there is an exponential increase in risk of adrenal suppression. This suggests 500mcg/day of fluticasone propionate should be the upper dose limit for children with asthma (51). Thus, in children who are not adequately controlled on 200mcg/day of fluticasone propionate or equivalent doses of other inhaled corticosteroids (once other factors contributing to poor asthma control – including adherence, inappropriate delivery device and inhaler technique - have been excluded) the addition of other preventive therapy should be considered as an alternative to increasing the inhaled corticosteroid dose.

Role of additional preventive medication

The most common medication to be added to inhaled corticosteroids is a long-acting beta-agonist, usually as a single combination medication. Unfortunately there have been limited paediatric studies examining the addition of long-acting beta-agonist to inhaled corticosteroids for persistent asthma in children, and these form the basis of a recent Cochrane review (74). A total of 25 randomised trials, representing 31 control-intervention comparisons, and 5572 children, were included in the review. No studies included children less than 4 years of age. There were 24 comparisons of the addition of long-acting beta-agonist to placebo, while the dose of inhaled corticosteroids was



held constant. These demonstrated no significant reduction in exacerbation rate (patient-important outcome measure), but an improvement in lung function (surrogate outcome measure), as expected in patients taking long-acting beta-agonists. Seven studies compared the addition of long-acting beta-agonist to an increased dose of inhaled corticosteroid. The long-acting beta-agonist treated group had a non significant increase in exacerbations requiring oral steroids and hospitalisation, but significantly improved lung function and short term linear growth. The authors concluded the need to further examine the possibility of an increased risk of rescue oral steroids and hospital admission with long-acting beta-agonist therapy (74). This observation is consistent with the findings of a meta-analysis demonstrating an increased risk of severe and life-threatening asthma exacerbations, as well as asthma related deaths, in patients using long-acting beta-agonists (75), although many of the patients were older and not receiving concurrent inhaled corticosteroids. A further recently published meta-analysis confirmed this increased risk for asthma-related intubations and deaths, even when long-acting beta-agonists were used with concomitant inhaled corticosteroids (76). This increased risk of exacerbations could be due to the development of tolerance to short-acting beta-agonists, resulting in a diminished response to the child's normal rescue therapy. Tolerance to short-acting beta-agonists has also been observed with regular long-acting beta-agonist use in other studies (23,25,26). An additional Cochrane review examined the addition of inhaled long-acting beta-agonists to inhaled corticosteroids as first line therapy for persistent asthma in steroid-naïve adults and children (77). This review concluded that the current evidence does not support the use of combination therapy as first line preventive treatment, without a prior trial of inhaled corticosteroids (77). The results of a recently published study comparing treatment options as step-up therapy for



children with uncontrolled asthma while receiving inhaled corticosteroids (78) also provides important new information. This randomised crossover study in 182 children aged 6-17 years of age who had uncontrolled asthma on 100mcg of fluticasone propionate twice daily received the following 3 therapies in random order over 16 weeks: 250mcg of fluticasone propionate twice daily (ICS step up), 100mcg of fluticasone propionate plus 50mcg salmeterol twice daily (LABA step up) and 100mcg of fluticasone propionate twice daily plus 5 or 10mg montelukast daily (LTRA step up). Although overall the LABA step up was more likely to provide the best response, many children had a best response to ICS or LTRA step up, highlighting the need to regularly monitor and appropriately adjust each child's therapy (78). This difference in the effectiveness of the addition of long-acting beta-agonists in children versus adults was again highlighted in a Cochrane review of the addition of long-acting beta-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma and sub-optimal control on low dose inhaled steroids (79). In adolescents and adults the combination of LABA and ICS was modestly more effective in reducing the risk of exacerbation requiring oral corticosteroids than a higher dose of ICS. However in children combination therapy did not lead to a significant reduction but rather a trend to an increased risk of oral-steroid treated exacerbations and hospital admission. The authors concluded that these trends raised concerns about the safety of combination therapy in children under the age of 12 years (79). These recent publications (74,77,78,79) support the current NAC recommendations of reserving the addition of long-acting beta-agonists to children not adequately controlled on 200-250mcg/day of fluticasone propionate or HFA beclomethasone dipropionate (or 160mcg ciclesonide) or 400-800mcg/day of budesonide (5), as well as highlighting the potential role of montelukast as an



alternative add on therapy. While Symbicort Maintenance and Reliever Therapy (SMART) is approved for patients aged 12 years and over, there is currently only limited paediatric data available (80). Despite the current evidence and NAC recommendations as well as age restriction on prescribing of long-acting beta agonists (salmeterol \geq 5 years; eformoterol \geq 12 years), combination medications now represent around 40% of the preventer market, and have been prescribed to around 20% of pre-schoolers with asthma (81). This overuse of a product with limited evidence of efficacy in children, but the potential for significant side effects, and substantially more costly than low dose inhaled steroids is of major concern, particularly in light of the evidence that low dose inhaled steroids have been shown to provide adequate control for the vast majority of children with persistent asthma. In the absence of data showing the safety and efficacy of long-acting beta-agonists in children under the age of 4 years, the 2009 revision of the GINA guidelines for the diagnosis and management of asthma in children 5 years and younger (4) specifically state that the use of long-acting beta-agonists or combination therapy can not be recommended and their use is not included as a treatment option. In addition a recent statement by the FDA also highlights the ongoing safety concerns of long-acting beta-agonists particularly in children, recommends their use only as combination therapy in paediatric and adolescent patients to ensure compliance with both treatments and highlights the need to limit exposure to long-acting beta-agonists by attempting to withdraw them again once good asthma control has been achieved (82).

As highlighted earlier in this article an additional benefit of montelukast is its proven efficacy for protecting against exercise induced bronchoconstriction (20,21). When used as regular treatment it has been shown to be more effective than long-acting beta-agonists for protection against exercise induced bronchoconstriction in both



adults (22,23) and children (24-26). In addition the recently published crossover study comparing various step up options for children uncontrolled on inhaled corticosteroids has also highlighted that many children do better on LTRA add on compared to LABA add on (78). Further, in contrast to regular long-acting beta-agonist use, montelukast is not associated with the development of tolerance to either protection against exercise induced bronchoconstriction, nor response to short acting beta agonists (23,25,26). Montelukast has now been approved in Australia as a PBS subsidised medication for add on treatment (as an alternative to long-acting beta-agonists) for children aged 6-14 years, who despite inhaled corticosteroids, have ongoing activity related asthma. In children 2-5 years of age, as mentioned previously, the patient will need to pay full price if montelukast is used as add on therapy.

Another medication with a potential “steroid sparing” benefit is low dose theophylline, the addition of which has been shown to be as effective as doubling inhaled corticosteroid dose in adults (83).

Systemic Corticosteroids

The majority of children with persistent asthma requiring preventive treatment can be managed on regular inhaled corticosteroids, with or without a long-acting beta-agonist or leukotriene receptor antagonist. 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) for inhaled corticosteroids has been demonstrated to be around 400-800 mcg/day for budesonide and 250-500 mcg/day for fluticasone propionate (and it is assumed to be a similar dose, 250-500 mcg/day for HFA-beclomethasone dipropionate). Once these limits are reached, it is important to consider issues such as



correct diagnosis, adherence, inhaler technique, and psycho-social issues, as well as other pharmacological and non-pharmacological options such as smoking cessation in the parents or older child or allergen avoidance. 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, given their significant potential for side effects.



TREATMENT OF ACUTE ASTHMA

Systemic Corticosteroids

Efficacy

Systemic corticosteroids have been shown to improve outcome in hospitalised children with acute asthma, including earlier discharge and fewer relapses (84). Early use of systemic corticosteroid therapy in acute exacerbations of asthma in adults and children, reduces hospital admissions and also prevents relapse in the emergency department setting (85,86). A comparison of a single oral dose of 2mg/kg prednisolone and 2mg fluticasone via an MDI and spacer in children with severe acute asthma in the emergency department setting demonstrated a significant reduction in hospitalisation in the prednisolone treated patients (87). A recent study has however questioned the efficacy of systemic steroids for preschool children presenting to hospital with acute mild-moderate virus induced wheezing (88). A 5 day course of prednisolone (10mg daily for 5 days for children 10-24 months and 20mg daily for older children) was no different to placebo in terms of duration of hospitalization or other outcomes.

A recent systematic review of parent-initiated oral corticosteroid therapy for intermittent wheezing illnesses in children concluded that there was limited and inconclusive evidence available for this common practice (89). These variable responses may be explained by variations in age and clinical pattern of wheezing. Oommen et al (90) assessed the efficacy of a short-course of parent-initiated oral prednisolone 20mg once daily for 5 days for viral wheeze in children aged 1-5 years and found no benefit over placebo in terms of symptom severity over a 7 day period. In contrast a recently published study in 6-14 year old children with acute asthma



demonstrated a modest improvement with parent-initiated oral corticosteroids when compared to placebo (91). Therefore, parent-initiated oral corticosteroid therapy cannot be recommended in preschool children, but may have a role in the management of older children.

Indications

Systemic corticosteroid therapy should be considered in children with acute episodes of asthma whose response to treatment with a beta-agonist is poor (less than 4 hours relief) or those who require frequent treatment with a beta-agonist (every 4 hours) for 36-48 hours. In general this means that any child with moderate to severe acute asthma based on NAC criteria (5) should receive systemic steroids.

Table 2. Initial assessment of acute asthma in children
(Adapted from NAC Asthma Management Handbook 2006 [5] with permission)

Symptoms	Mild	Moderate	Severe and life-threatening*
Altered consciousness	No	No	Agitated Confused/drowsy
Oximetry on presentation (SaO ₂)	94%	94–90%	Less than 90%
Talks in	Sentences	Phrases	Words Unable to speak
Pulse rate	< 100 beats/min	100–200 beats /min	> 200 beats/min
Central cyanosis	Absent	Absent	Likely to be present
Wheeze intensity	Variable	Moderate to loud	Often quiet
PEF**	> 60% predicted or personal best	40–60% predicted or personal best	<40% predicted or personal best Unable to perform
FEV ₁	> 60% predicted	40–60% predicted	< 40% predicted Unable to perform

*Any of these features indicates that the episode is severe. The absence of any feature does not exclude a severe attack.

**Children under 7 years old are unlikely to perform PEF or spirometry reliably during an acute episode. These tests are usually not used in the assessment of acute asthma in children.



Given the recent study which failed to show any benefit of oral steroids in preschoolers with intermittent viral induced wheezing (88), the use of systemic corticosteroids in pre-school children, particularly those with intermittent viral induced wheezing, should be limited to those with wheeze of such severity that they need to be admitted to hospital i.e those with at least moderate but generally severe acute wheeze. This recommendation has also been supported in a recent publication which advocates that short burst oral steroid must not be given in the community setting for attacks of preschool viral wheeze and should be considered for only a minority of preschool children admitted to hospital such as those with features strongly suggestive of atopic wheeze or those with very severe bronchodilator-unresponsive wheeze (92).

Dosage

The systematic review of corticosteroids for hospitalised children with acute asthma highlighted the need for further studies to clarify optimal dose and route of administration for corticosteroids (84) Given that the majority of studies have used 2mg/kg oral prednisolone (84,87), our current recommendation in children would be a dose of 2mg/kg of oral prednisolone (maximum 60 mg) given initially and subsequently daily doses of 1mg/kg if required. Duration of therapy will generally be up to 3 days (a 5 day course has not been shown to confer any advantage over a 3 day course in non hospitalized children [93]), but in patients with severe persistent asthma or those with severe or life threatening acute asthma, a more prolonged course may occasionally be needed with tapering of the dose to prevent asthma relapse. Although a recent comparison of oral dexamethasone(0.6mg/kg) with oral prednisolone (2mg/kg) demonstrated that a shorter course of dexamethasone provided equal benefit and was better tolerated (94), concerns were raised about the greater potential



for adrenal suppression with dexamethasone related to its longer half-life. (95). While there appears to be no definite advantage of parenteral over oral corticosteroids (84) intravenous corticosteroids (methylprednisolone in an initial dose of 2mg/kg, up to 60mg, subsequent doses 1mg/kg every 6 hours on day 1, then every 12 hours on day 2, then daily) will be needed if the child is extremely ill, unconscious, or cannot tolerate oral medication. Hydrocortisone 8-10mg/kg (max 300mg) initially then 4-5mg/kg/dose can be used as an alternative parenteral corticosteroid.

Side Effects

The side effects of systemic corticosteroids are well documented (96) and risks are related to dosage and duration of usage. Using HPA axis suppression as an index of systemic toxicity, single bursts of up to 2 weeks (97,98) do not reduce adrenal response. However 20% of children having four or more bursts per year demonstrate suboptimal adrenal response (98). In addition follow up of the patients in the Childhood Asthma Management Program (CAMP) study demonstrated that multiple oral corticosteroid bursts over a period of years can produce a dosage-dependent reduction in bone mineral accretion and increased risk in osteopenia in boys, but not girls (70). Other rare problems with systemic steroid therapy include acute steroid induced myopathy (99,100) and anaphylaxis after intravenous hydrocortisone (101,102).

Inhaled Corticosteroids

High dose inhaled corticosteroids (1600-2250 mcg/day) provide a partially effective strategy for the treatment of episodes of intermittent viral induced wheezing, with some reduction of oral corticosteroid requirements (17). Although one study in children with moderate acute asthma demonstrated high dose inhaled corticosteroids to be as effective as oral prednisolone (103), another study in children with more



severe acute asthma demonstrated oral prednisolone was superior to inhaled corticosteroids. (87). A systematic review on the early use of inhaled corticosteroids in the emergency department treatment of acute asthma in both children and adults concluded that although inhaled steroids reduced admission rates, there was insufficient evidence that they provided a clinically important change in pulmonary function or clinical scores, or that inhaled corticosteroids alone were as effective as systemic steroids (104). A recent study of high dose fluticasone used preemptively in preschool children with intermittent virus-induced wheezing demonstrated a significant reduction in the need for rescue systemic corticosteroids (8% fluticasone versus 18% placebo) but children treated with fluticasone had a significantly smaller gain in height and weight (105). The authors concluded that given the potential for overuse, this preventive approach should not be adopted in clinical practice until long-term adverse effects are clarified (105). Intermittent inhaled corticosteroid therapy for infants with wheezing episodes had no effect on the progression from intermittent to persistent wheezing and no short-term benefit during episodes of wheezing in the first 3 years of life (106). While short-course montelukast and low dose inhaled steroids given for at least 7 days at the time of asthma exacerbation in children with intermittent asthma has also been shown to provide some benefit in reducing the severity of the exacerbation (18,19), there was no significant difference in systemic steroid use when compared to placebo. A recent study which compared 5 daily treatments of montelukast and prednisolone in children discharged home from the emergency department following a presentation with asthma, demonstrated a higher treatment failure rate with montelukast (22.4%) compared with prednisolone (7.9%), although no placebo arm was included and almost 80% of montelukast treated children had a successful treatment outcome (107). The only paediatric study to have



investigated a doubling of inhaled corticosteroids during an acute exacerbation, which has often been incorporated into asthma action plans, failed to show any benefit (108). In conclusion while there is some evidence supporting both high dose inhaled corticosteroids as well as intermittent montelukast and low dose inhaled steroids in the treatment of acute asthma, short course oral corticosteroids remain the preferred option because of ease of administration, relative cost and their greater efficacy in severe acute asthma. However both oral and inhaled steroids have the potential for long term side effects which appears to depend on the cumulative dose.

CONCLUSIONS

Inhaled corticosteroids (ICS) have proven efficacy in the preventive treatment of persistent asthma in children. This assumes that the appropriate patients are targeted and the dose is titrated against clinical benefit and risk of side effects. The addition of long-acting beta-agonists (LABAs), usually as combination therapy, should only be considered if children fail a trial of inhaled steroids. In the absence of evidence of safety and efficacy, the use of LABAs is not recommended in children under the age of 5 years. In children with ongoing problem with exercise induced symptoms, despite inhaled corticosteroids, the addition of leukotriene antagonists have been shown to be effective. The evidence is less clear for the efficacy of inhaled corticosteroids in children with intermittent viral induced wheezing which is the most common pattern of wheezing in the preschool years. Thus, leukotriene receptor antagonists should be first line preventive treatment for children with frequent intermittent wheezing or mild persistent asthma. The recommendations for the use of inhaled corticosteroids in the preventive treatment of childhood asthma appear in Table 1. There is also proven efficacy of systemic corticosteroids in the treatment of acute asthma in children



although their benefit for preschool children with intermittent viral induced wheezing has not been demonstrated. The role of intermittent inhaled corticosteroids in the management of acute exacerbations in children requires further evaluation. Our recommendations for the use of corticosteroids for acute asthma in children are summarised in Table 2.

Background and evidence base of recommendations

This position statement was revised by the authors following approval from 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 Paediatric Special Interest Group of the TSANZ 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. Following its endorsement by the TSANZ it was submitted to the MJA.

The recommendations are based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence for clinical guidelines (109-112). This divides recommendations into STRONG or WEAK based on the quality of evidence, the balance between desirable and undesirable effects, values and preferences and cost (resource allocation) [112].

The implications of a STRONG RECOMMENDATION are (112):

- For patients – most people in your situation would want the recommended course of action and only a small proportion would not; request discussion if the intervention is not offered.
- For clinicians – most patients should receive the recommended course of action.



- For policy makers – the recommendation can be adopted as a policy in most situations.

The implications of a WEAK RECOMMENDATION are (112):

- For patients – most people in your situation would want the recommended course of action but many would not.
- For clinicians – you should recognize that different choices will be appropriate for different patients and that you must help each patient to arrive at a management decision consistent with her or his values and preferences.
- For policy makers – policy making will require substantial debate and involvement of many stakeholders.

In addition to providing a recommendation based on the GRADE system, the GRADE quality of evidence classification (110) is also provided alongside the strength of the recommendation and has the following implications:

- High quality evidence – Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality evidence – Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality evidence – Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality evidence - Any estimate of effect is very uncertain.



Table 1

Recommendations for the use of inhaled corticosteroids in the preventive treatment of childhood asthma.

1. Inhaled corticosteroids (ICS) are indicated as first line preventer treatment in children with moderate to severe persistent asthma or as an alternative to non steroidal preventers in frequent intermittent or mild persistent asthma. Based on current evidence, it is preferable to trial non steroidal preventers first in frequent intermittent or mild persistent asthma and proceed to ICS if there is poor response after 2-4 weeks. (STRONG Recommendation, HIGH QUALITY Evidence)
2. The dose of inhaled corticosteroid needs to be titrated against disease severity of (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 mcg/day of BUD or 200 mcg/day of FP or HFA-BDP or 160mcg/day Ciclesonide (CIC) (in children 6 years and over) will achieve control in the majority of children. (STRONG Recommendation, HIGH QUALITY Evidence)
3. The need for high dose inhaled corticosteroids (> 400 mcg/day BUD or 200-250 mcg/day FP or HFA-BDP in children 5 years or younger or > 800 mcg/day BUD or 400 - 500 mcg/day FP or HFA-BDP or 320mcg/day CIC in children over 5 years of age) is an indication for specialist assessment. (STRONG Recommendation, MODERATE QUALITY Evidence)
4. Dose dependent systemic activity has been demonstrated for inhaled corticosteroids, although significant clinical side effects are unusual. Short term linear growth suppression has been demonstrated in children, but minimal long term effects on growth or bone density have been reported to date. Nevertheless



monitoring of growth is recommended in children on inhaled corticosteroids.

(STRONG Recommendation, MODERATE QUALITY Evidence)

5. Manoeuvres to decrease oro-pharyngeal 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. However this will also result in improved efficacy which is likely to allow a reduction in inhaled steroid dose. (STRONG Recommendation, HIGH QUALITY Evidence)
6. In situations where effective control of asthma cannot be achieved with doses of 400 mcg/day BUD, or 200 mcg/day FP or HFA-BDP or 160mcg/day CIC, the main step up options include increasing the inhaled steroid dose or the addition of a long-acting beta-agonist (LABA) or a leukotriene antagonist. In the absence of evidence of safety and efficacy, the use of LABAs is not recommended in children aged 5 years or younger. (STRONG Recommendation, MODERATE QUALITY Evidence) In children with ongoing problems with exercise induced symptoms, despite inhaled corticosteroids, the addition of leukotriene antagonists have been shown to be effective and superior to long-acting beta-agonists, and do not have the problem of the development of tolerance.(STRONG Recommendation, MODERATE QUALITY Evidence)
7. Rarely, long-term systemic corticosteroids may be needed in children with severe persistent asthma who remain poorly controlled despite high dose inhaled corticosteroids and long-acting beta-agonists. (WEAK Recommendation, LOW QUALITY Evidence) Specialist referral is strongly recommended before commencing such therapy. (STRONG Recommendation, MODERATE QUALITY Evidence)



Table 2

Recommendations for the use of corticosteroids in the treatment of an acute asthma exacerbation in children.

1. In general systemic corticosteroid therapy is recommended for children assessed as having a moderate-to-severe acute asthma exacerbation, or if there is incomplete response to beta-agonists. (STRONG Recommendation, HIGH QUALITY Evidence)
2. The use of systemic corticosteroids in pre-school children, particularly those with intermittent viral induced wheezing, should be limited to those with wheeze of such severity that they need to be admitted to hospital i.e. those with at least moderate but generally severe acute wheeze. (STRONG Recommendation, MODERATE QUALITY Evidence)
3. An initial dose of 2mg/kg prednisolone (maximum 60 mg) orally is recommended, followed by daily doses of 1mg/kg if required. While a 3 day course is generally sufficient, in severe cases a more prolonged course may be indicated. (STRONG Recommendation, MODERATE QUALITY Evidence)
4. Intravenous corticosteroids may be indicated if oral therapy is poorly tolerated or the child is critically ill. Methylprednisolone should be used in an initial dose of 2mg/kg (maximum 60mg) with subsequent doses 1mg/kg every 6 hours on day 1, then every 12 hours on day 2, then daily. Hydrocortisone 8-10mg/kg (max 300mg) initially then 4-5mg/kg/dose can be used as an alternative parenteral corticosteroid. (STRONG Recommendation, LOW QUALITY Evidence)



5. While oral corticosteroid therapy of less than 2 weeks duration carries little risk of long term HPA axis suppression, frequent courses (four or more per year) may carry a cumulative risk. In addition there may be cumulative effects on bone mineral accretion particularly in boys. (STRONG Recommendation, MODERATE QUALITY Evidence)
6. The need for recurrent systemic corticosteroid therapy requires reassessment of the interval therapy of the child (particularly in those with persistent asthma) and specialist referral. (STRONG Recommendation, LOW QUALITY Evidence)
7. While there is some evidence for the benefit of intermittent inhaled corticosteroids and leukotriene receptor antagonists in acute asthma, oral corticosteroids remain the treatment of choice. This is particularly true for more severe episodes, because of ease of administration, cost, and greater proven efficacy in severe acute asthma. (STRONG Recommendation, MODERATE QUALITY Evidence)



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