**Inhaled corticosteroids and growth – a review**

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**Abstract**

**Objective**: the aim of this review was to evaluate the medical literature in the last 10 years regarding the impact of the use of inhaled corticosteroids in children’s and adolescents’ growth.

**Methods**: literature review.

**Results**: the use of inhaled corticosteroids in childhood asthma in dosages appropriate to its severity does not seem to impair adult height.

**Conclusions**: the use of inhaled corticosteroids in childhood asthma does not seem to impair growth. However, it is prudent to use the lowest possible dose necessary to achieve a good clinical control of asthma, as well as to monitor the growth of any child/adolescent receiving inhaled corticosteroids.


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**Introduction**

Inhaled corticosteroids (ICS) have been used for more than 20 years as the most efficient prophylactic treatment for patients with asthma. Its efficacy is unquestionable. There are, however, concerns about its side effects, especially about its potential impact on children’s and adolescents’ growth. New methods to quantify linear growth have been developed lately to assess the risk for growth suppression. Although a large number of studies on this topic have been published, the discussion of this question is far from over.

**Factors that influence normal growth**

Normal growth depends on the complex interaction of hormonal influences, nutrition and tissue response. Adult height is determined by: 1) growth during the first 2-3 years of life, which is primarily determined by nutrition; 2) growth from 3 years of age through puberty, which depends on secretion of growth hormone by the pituitary gland; and 3) growth during puberty, which depends on the action of growth hormone and sexual glucocorticoids.³ Growth does not take place at a constant rate over any given year,²,³ but, rather, shows cyclic and seasonal variability.³⁻⁷ Intervals of 2 or more years without growth may occur.⁶ General growth is non-linear and rhythmic, and each body segment has its own rhythm of endogenous growth.⁴,⁷ Therefore, growth interruption phases may easily confuse the clinician and lead to the conclusion that the child is not growing at all, especially when this interruption affects children with a short parental height.⁶ Reductions in the velocity of linear growth in 1 year are not necessarily followed by decrease of this velocity in the subsequent year, and vice-versa.⁶⁻⁸ Records of the velocity of linear growth in 3 years explain 34% of the final height variation,⁶⁻⁸ while the velocity of leg growth in 1 month explains virtually nothing of the variation in the velocity of annual height growth.⁸

Asthma, as well as other chronic diseases, may sometimes be associated with late puberty, which may simulate growth
delay. This fact is not associated with the disease severity or treatment.1,7-19 Growth delay in asthmatic children is associated with delayed bone maturation, and height-for-age remains compatible with skeletal age.7,17,20 Therefore, growth can “catch up”, and normal or expected final adult height can be attained.7,13,14,19,20

**Growth assessment methods**

ICS effects on growth may be assessed in short-, intermediate-, and long-term studies. Long-term studies assess growth from infancy or childhood through final adult height. Intermediate-term studies assess growth in periods longer than 6 months, but do not include final height. Short-term studies observe growth for up to 6 months.1-8

Many short- or intermediate-term studies about the effect of ICS on growth use **knemometry** to assess growth. According to reports, knemometry, devised in the early 80s by Valk, can detect real changes in leg growth in short periods of time, even on a single day.5,21,22 There are, however, a significant number of potentially confusing factors that may affect the accuracy of knemometry. As height is reduced approximately 1 cm during the day due to articular cartilage compression, measurements must be made in the early evening of the same day of the week during the period of observation.5,21,24,25 Growth rates for the different parts of the body are different and so there is no correlation between leg growth and total height in a period of 6 months.8,22 Moreover, after a 1-hour rest, knemometric measurements may show an increase of 2 mm, which is the same as the average rate of leg growth in a month.8 Also, the standard error for height measurement, even for experienced observers, is 0.3-0.4 cm in very young children.6,26 Therefore, short-term knemometry may exaggerate the effect of ICS on growth delay.1,18 Knemometry reports of apparently reduced growth associated with asthma treatment should be carefully interpreted.5,26 If the results of a short-term study were extrapolated to years, the expected height would fall from the 50th to the 25th or 3rd percentile according to some studies.18 Effects of such magnitude have not been observed in clinical practice or confirmed in long-term studies.3,18,27 Intermediate-term studies with preschool children are complicated by the fact that the measurement technique may vary according to the age.6

Knemometry fails to predict long-term growth,3,7,8,21,25,27 and the observed final height to expected final height ratio is the only reliable variable for human growth measurement, considering gender differences and average parental height.1,6-8

Long-term studies usually use stadiometry to assess growth. Stadiometry consists of a device usually mounted against a wall that, if regularly maintained and calibrated, provides accurate measurements of height.9,23,28-31 Stadiometry is a relatively inexpensive method and requires little formal training. It does not provide immediate answers about growth rates, but it does provide useful information about long-term growth.28

Radiographic studies may also be used to determine skeletal age and predict final height.29,31 Radiographs of the left hand and wrist are used to determine skeletal age by comparison with the norms published by Greulich & Pyle.29,30 Tanner et al.30 developed an alternative method for the assessment of skeletal age, which consists of radiographs of 20 separate bones, including legs and spine. This technique was adapted to computerized assessment. It is a more expensive method of skeletal age assessment, but provides an accurate assessment of potential growth, while the hand is not representative of the height of a person.29,30

Both methods have caveats: experience is necessary to determine skeletal age, and normal rate of skeletal maturation varies according to ethnicity and gender. Moreover, Greulich & Pyle’s norms, as well as Tanner-Whitehouse’s, were developed for normal children and can not be used for children with several types of growth delay.29,30

**Effects of asthma treatment on growth**

Studies have shown that non-corticoid asthma treatments, such as beta2-adrenergic agonists, may inhibit the growth hormone axis,6,17,32 while ICS do not affect secretion of growth hormone or insulin-like growth factor.5,33-35

Optimal clinical control of most children with moderate asthma is obtained with 100-400 mcg/day ICS doses (depending on type of ICS and inhalation device).7,11,13-15,17-19,25,36-40 A growth spurt after ICS treatment initiation (presumably due to better control of asthma) has also been observed.11,36 Studies that report growth delay used ICS doses that frequently seem excessive.14 Some authors consider an ICS dose of or higher than 800 mcg/day as the threshold for growth suppression,28,41,42 and further argue that administration of a high dose of ICS once a day has less impact on growth than the administration of ICS in 2 or 3 daily doses.41

It is interesting to note that growth does not seem to be suppressed by the use of ICS in severe asthma,43 and that undesirable systemic effects are more noticeable in healthy volunteers than in asthmatic patients, depending on the form of ICS administration (nebulization, aerosol, dry powder), for either a single type of ICS or for different types.44

According to some case reports,45-48 a few patients may undoubtedly present significant growth delay in association with ICS use,18 maybe as a result of individual sensitivity. This fact should alert clinicians to the need to carefully monitor all patients on ICS.1,17,18 The aim of every treatment17,18,40 should be to determine the minimum necessary dose for good clinical control of the disease.

Table 1 summarizes 30 studies,49-78 most of them short- and intermediate-term.49-72,74-78 Only one includes the use of triamcinolone acetonide (TAA).49 all the others assess
beclomethasone dipropionate (BDP), budesonide (BUD), or fluticasone propionate (FP) alone or in association with other ICS, bronchodilators, or sodium cromoglycate (SCG). Fifteen studies in this table show growth delay in association with the use of ICS,64-78 while 15 studies report that there was no significant delay in growth.49-63

Nina & Russe53 assessed the effect of BDP and BUD treatment on growth. Fifty-eight prepubertal children with severe chronic asthma were followed for an average of 2.7 years (1-5.1 years) while using BDP or BUD (average daily dose = 800 mcg/day). Children with well-controlled asthma grew up well, while those with poorly controlled asthma grew very little, whether they were receiving ICS or not. Volovits et al.55 followed 15 children with severe persistent asthma treated with BUD (200 mcg/day) for 3 to 5 years. Average height was measured by stadiometry. All children grew and gained weight normally. Their skeletal age advance was parallel to their chronological age. Moreover, asthma was well controlled according to the physician’s assessment and the parents’ observations. Ruiz and Price56 studied the effect of ICS on the growth of young asthmatic patients. They studied 18 asthmatic children (ages 4.5 to 7.4 years) using BUD via Nebuhaler in initial doses of 400 mcg/day and subsequent doses of 200-800 mcg/day. None of the children was making regular use of oral corticosteroids, or had recently received a short course of prednisolone for asthma exacerbation. Height was measured with stadiometry, and skeletal age was assessed radiographically. No delay in growth was observed, and a discreet delay in skeletal age was not associated with ICS treatment. The decreased systemic effect of ICS in this study was attributed to the use of high volume spacers. A 1-year study59 compared the effects of FP 50 mcg twice daily with SCG 20 mcg four times daily in children with mild asthma. This study reported normal growth in both groups. All subjects were prepubertal children (4-10 years of age). Height was measured by stadiometry. As additional information, this study found that pulmonary function improved more significantly in patients treated with FP than in those on SCG. A double-blind study62 of 325 prepubertal children with persistent asthma (boys: 4-11 years; girls: 4-9 years) on placebo or FP 100 or 200 mcg/day was carried out for 1 year. Stadiometry was used for height measurements and skeletal age was radiographically assessed monthly. Adherence to treatment was controlled at each visit by counting dosage packs the patient had used. Practically all patients in the three groups grew normally during the study. Skeletal maturation was compatible with chronological age in all the groups.

In another study, 195 children aged 6 to 16 years were followed up for 1 year. They had mild or moderate asthma and were using 84 mcg BDP four times daily, or slow-release theophylline twice daily in doses adjusted for optimal control of symptoms. Stadiometry was used to measure height. Growth was assessed from different perspectives: for each height recorded, the standard deviation scores were calculated and compared with scores for same-age population; height velocity was calculated in centimeters per year for 1 year before ICS treatment, and subsequently calculated for each year during treatment; standard deviation values for height velocity were calculated in the same way as height standard deviation. Absolute height measurements during the course of treatment did not show differences for each group. However, reduction in growth velocity was observed in children using two BDP sprays four times daily. Therefore, the authors report that their results were not conclusive as to whether BDP therapy affects final height. For 1 year, Simons75 followed 241 children (average age [± Standard Deviation] 9.3 [±2.4] years) with clinically stable asthma in a randomized double-blind study. The children used 200 mcg/day BDP twice daily, 50 mcg salmeterol xinafoate (SX) twice daily, or placebo. Although BDP proved to be more efficient in controlling symptoms, children on this regimen showed a statistically significant delay in growth. Height was not measured after the treatment was discontinued. Another 1-year study77 measured growth velocity in 55 prepubertal children with stable asthma. Ages ranged from 4.4 to 11 years. Thirteen children did not receive ICS; 19 received BUD, 20 received BDP, and 4 received ICS and prednisolone. Average doses were higher than 700 mcg/m²/day for the children in the BDP group, and higher than 500 mcg/m²/day for those in the BDP group. Slow growth was observed in the children treated with ICS and oral corticosteroids. Heuck et al.78 conducted a knemometry short-term study. Twenty-four children, ages 5.6-12.5 years, received 400 mcg BUD twice daily or 800 mcg BUD in a single daily dose in the morning. The average rate of leg growth decreased during administration of 400 mcg BUD twice daily, which did not happen during the administration of 800 mcg BUD in a single daily dose.

Most studies that reported no evidence of growth delay had follow-ups of 1 year or longer, while most of those that documented growth delay were short- or intermediate-term studies, ranging from periods as short as 18 days to 12 months. Several researchers point out that their short-term studies may not be good predictors of long-term growth rates,67-69,72,74,76 or that the differences observed may the assigned to late puberty 64, or, still, that the potential adverse effects of uncontrolled severe asthma are higher than any possible side effect of ICS therapy.71

Table 2 summarizes nine studies that reported growth delay depending on the ICS dose administered.79-87 Growth delay was not observed in maximum doses from 400 to 800 mcg/day, no matter what type of ICS was studied. The form of ICS administration varied from study to study, which may have potentially affected results. Some studies found that growth “caught up” after transition to FP.81,83

Agertoft & Pedersen,80 in a controlled prospective study of 216 asthmatic children receiving BUD or no ICS, concluded that BUD doses ≤ 400 mcg/day did not delay growth, while doses higher than that were associated with a significant reduction in height velocity. McCowan et al.85
Table 1 - ICS and effects on growth

<table>
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<tr>
<th>Study</th>
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<tr>
<td>Brown et al. 1989</td>
<td>Five 1 yr.; open clinical trials;</td>
<td>82; average age 11.0 +/-0.24 yr.</td>
<td>TAA 400 mcg/day during 1-8 weeks; maximum daily dose at end of study; 1200 mcg</td>
<td>After 6 months, patients grew an average 2.53 cm compared with predicted growth of 2.76 cm. After 12 months, real and predicted height growths were 5.19 and 5.67, respectively</td>
<td>Children grew at a rate not significantly different from rates predicted for a healthy, normal population</td>
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<td>Russel et al. 1989</td>
<td>Open study; 18 mo.</td>
<td>50; age 2-12 yr.</td>
<td>BUD</td>
<td>No effects on growth</td>
<td>Poorly controlled asthma is associated with delay in growth</td>
</tr>
<tr>
<td>Pritts et al. 1993</td>
<td>Follow-up study; 30 days; staging;</td>
<td>48; group I: no ICS, some took SCG; group II: BDP</td>
<td>BDP 200-900 mcg/day (average 400 mcg/day), inhaler (spray)</td>
<td>No significant height standard deviation values for the 2 groups when compared to each other or to normal population</td>
<td>Cause of delayed growth and puberty frequently observed in asthmatic children may be attributed to low production of adrenal androgens</td>
</tr>
<tr>
<td>Varsano et al. 1990</td>
<td>Open-label trial; 1 yr.; severe asthma; staging</td>
<td>16; average age 4 yr.11 mo. (3.5 - 7 yr.)</td>
<td>BUD 800 mcg/day, inhaler with spacer</td>
<td>Patients with well-controlled asthma grew well, while those whose asthma was not well controlled grew poorly, no matter whether on ICS or not</td>
<td>Growth suppression in asthmatic children probably caused by poor control of disease rather than by ICS administration</td>
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<td>Merkus et al. 1993</td>
<td>Randomized placebo-controlled double-blind study; average 22 mo.; adherence to treatment monitored (74%)</td>
<td>40; average age 12.8 yr. (12-16 yr); 80 normal controls</td>
<td>BUD 600 mcg/day, inhaler without spacer</td>
<td>There was no reduction in growth velocity</td>
<td>Delayed growth observed in adolescents with asthma may be caused by delayed puberty, but not by administration of BUD 600 mcg/day</td>
</tr>
<tr>
<td>Volovitz et al. 1995</td>
<td>Open-label trial; 3-5 yr.; severe persistent asthma; staging</td>
<td>15; average age 4 yr. 10 mo. (2-7 yr.)</td>
<td>BUD 200 mcg/day, inhaler with spacer</td>
<td>No effect on growth</td>
<td>Treatment with inhaled BUD at a relatively low dose (200 mcg/day) for children with severe asthma is both safe and efficient</td>
</tr>
<tr>
<td>Ruiz &amp; Russel 1992</td>
<td>Open-label trial; 1 yr.; staging; adherence to treatment monitored</td>
<td>18; average age 5.6 yr. (4.5-7.4 yr.)</td>
<td>BUD 200-800 mcg/day, inhaler with spacer</td>
<td>No effect on growth</td>
<td>Children all used high-volume spacers, which have proven to decrease systemic influence of high ICS doses</td>
</tr>
<tr>
<td>Reid et al. 1996</td>
<td>Open-label prospective study; severe asthma; stadiometry and “minimeter”; treatment for 6 mo. to 1.5 yr.</td>
<td>40; average age 1.4 yr. (0.33-2.8 yr.)</td>
<td>Nebulized BU194 mg/day, with terbutaline or salbutamol</td>
<td>BUD therapy was associated with a minimum increase (statistically but not clinically significant) in linear growth</td>
<td>Study was limited by open design and by the fact that no satisfactory verification of adherence to treatment was carried out</td>
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<td>Konig et al. (abstract) 1996</td>
<td>Double-blind trial; 1 yr.; staging</td>
<td>325; age 4-11 yr.</td>
<td>Group 1: FP 100 mcg/day; Group 2: FP 200 mcg/day; Group 3: placebo; Diskhaler</td>
<td>No statistically significant difference between any dose of FP and placebo</td>
<td>It is generally agreed that poorly controlled asthma is the major determinant of poor growth</td>
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<tr>
<td>Price et al. 1997</td>
<td>1-yr. multi-center, open-label, randomized, parallel-group study; stadiometry; mild asthma</td>
<td>122; average age 6 yr. (4-10 yr.)</td>
<td>FP 100 mcg/day or SCG 80 mg/day, dry powder, Diskhaler and Sphinhalor, respectively</td>
<td>Neither drug was associated with growth delay</td>
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<td>Martinati et al. 1998</td>
<td>Prospective study; 7 mo.; staging; persistent asthma</td>
<td>48; average age 6.3 +/- 1.9 yr. (5-11 yr.)</td>
<td>BDP 150-700 mcg/day (average 276 +/- 124 mcg/day) or SCG 30-40 mg/day</td>
<td>All children grew according to normal growth expectations</td>
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<td>Visser et al. 1998</td>
<td>Open-label non-randomized trial; admission period 6 wk., followed by 2 wk. interval; knemometry every 2 wk.</td>
<td>21; age 6-10 yr.</td>
<td>FP 200 mcg/day, dry powder, inhaler</td>
<td>There was no effect on leg growth</td>
<td>As knemometry does not predict long-term linear growth, additional studies are necessary to assess effect of long-term use of this dose of FP</td>
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<td><strong>Studies that did not show delay in growth</strong></td>
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<tr>
<td>Allen et al. 1998</td>
<td>Randomized double-blind parallel-group placebo-controlled study; 1 yr; staging; persistent asthma</td>
<td>325; boys: 4-11 yr.; girls: 9 yr.</td>
<td>FP 100 mcg/day; FP 200 mcg/day; dry powder, Diskhaler</td>
<td>There was no significant growth delay</td>
<td></td>
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<tr>
<td>Hedlin et al. 1999</td>
<td>Randomized double-blind parallel-group placebo-controlled study; 10 days</td>
<td>40; 1-3 yr.</td>
<td>BUD 1600 mcg/day for 3 days and 800 mcg/day for 7 days, inhaler with spacer</td>
<td>No signs of growth delay were found</td>
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| **Studies that found evidence of growth suppression** |                                                                                |                         |                                                                          |                                                                        |                               |
| Delacourt et al. 1991      | Open-label study, average 19 mo.; severe asthma                                | 50; average age +/- SD: 10.8 +/- 2.9 yr. | BDP 750 to 1500 mcg/day                                                  | Only 6 of the 50 children (12%) presented decrease in the stature percentile, always less than 10 | Was growth delay a result of physiological deceleration of growth velocity in the pre-adolescent age? |
| Mackenzie & Wales 1991     | Double-blind placebo-controlled prospective study; knemometry; 1 mo.           | 13; age ?               | BDP 200 mcg/day; BDP 400 mcg/day                                        | Average leg growth rates were 0.38 mm/wk without ICS; 0.34 mm/wk with BDP 200 mcg; 0.2 mm/wk with BDP 400 mcg/day | At least short-term suppression of growth occurs with BDP > 400 mcg/day |
| Wolthers & Pedersen 1995   | Randomized double-blind crossover trial; 18-day treatment; 18-day interval; knemometry; mild asthma | 15; average age 9.5 yr. (6-13 yr.) | BUD 200 mcg/day and 800 mcg/day, inhaler with spacer                     | Average reduction in growth velocity during treatment was 0.11 mm/wk with 200 mcg and 0.36 mm/wk with 800 mcg BUD | BUD treatment is associated with short-term dose-dependent leg growth suppression in children with mild asthma |
| Wolthers & Pedersen 1992   | Double-blind placebo-controlled study; 12 wk.; weekly knemometry; mild asthma  | 43; average age 10.2 yr. (7-14 yr.) | BUD 200 mcg/day, 400 mcg/day, inhaler with spacer                       | BUD 800 mcg/day treatment was associated with reduction in leg growth velocity (but not for doses of 100 and 400 mcg/day) | High doses of BUD should be used only for children with severe asthma that can not be controlled with smaller doses of ICS in combination with other asthma therapies. Studies of short-term growth may not be good predictors of long-term growth rate |
| Wolthers & Pedersen 1995   | Randomized double-blind crossover study; sequence of 3 placebo- alternate active courses of treatment; knemometry; mild asthma; adherence monitored | 19; average age 10.7 yr. (7-14 yr.) | FP 200 mcg/day; BDP 400 and 800 mcg/day - dry powder inhaler          | Average leg growth velocity during treatment: FP 0.34 mm/wk, BDP 400 mcg 0.9 mm/wk, BDP 800 mcg 0.06 mm/wk | Higher growth rates with FP point to a significantly lower systemic effect of this drug. Short-term growth rates are not good predictors of long-term growth of normal children and of children with growth disorders |
| Tinkelman et al. 1993      | Randomized multi-center double-blind double-placebo-controlled trial; 1 yr.; mild to moderate asthma, staging | 195; average age 11.9 yr. (6-18 yr.) | BDP 340 mcg/day vs. theophylline                                        | Discreet reduction in growth velocity with BDP; more evident in boys | Whether BDP treatment affects a patient’s final height can not be concluded from findings |
| Hunt et al. (abstract) 1994 | Few details; staging; 9-12 mo. treatment                                       | 162 prepubescent children | BDP (dose?) dry powder and inhaler; SCG (dose ?)                       | Average growth velocity reduced with BDP; dose-dependent effect, more accentuated with dry powder |                               |
| Crowley et al. 1995        | Longitudinal study; 12 mo.; staging, hormonal studies                        | 56; average age 8.3 yr. (4.4-11.7 yr.) | Group 1: non-dependent corticoid (13); group 2: BUD 760 mcg/m² (19); group 3: BUD 560 mcg/m²/day (20); group 4: ICS+ prednisolone (4) | Sight linear growth delay in ICS groups; significantly higher in BDP + prednisolone group. Normal findings in hormone levels tested | Potential dangers of uncontrolled severe asthma are higher than any side effect that may be caused by treatment |
| Douil et al. 1995          | Double-blind placebo-controlled community-based study; 7 mo. treatment; 4-mo. interval; Raven Minimeter measurements | 50 BDP, 44 placebo; average age 8 yr. (7-9 yr.) | BDP 400 mcg/day, dry powder, Diskhaler                                 | Growth delay (BDP group > 1.0 cm less than placebo group); growth did not catch up during interval | Our findings for a 7-mo. treatment can not be extrapolated to long-term effects, as they would go against studies that show that the asthmatic child attains predicted height or at times even grows more than predicted |
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<tr>
<td>Saha et al.</td>
<td>Retrospective study; 5-yr. treatment with ICS; anthropometry; growth data before treatment analyzed</td>
<td>201; average age 4.4 yr (1-11 yr.)</td>
<td>BDP and BUD; average dose 500 mcg/m² (100-2500 mcg/day) dry powder or spray</td>
<td>Growth delay immediately after beginning of treatment, especially during 1st year</td>
<td>Growth delay was not dose-dependent</td>
</tr>
<tr>
<td>Verberne et al.</td>
<td>Randomized double-blind parallel-group study; mild to moderate asthma; 6-wk. admission period; 54-wk. treatment; 2-wk. follow-up after treatment; staging</td>
<td>67; average age 10.5 yr. (6-16 yr.)</td>
<td>Salmeterol 100 mcg/day or BDP 400 mcg/day, both Rotadisks with Diskhaler</td>
<td>Growth delay (1.4 cm) in BDP group, more accentuated in prepubescent children</td>
<td>It is unlikely that negative effects of ICS on height would last for longer periods during treatment</td>
</tr>
<tr>
<td>Simons 1997</td>
<td>Randomized double-blind placebo-controlled parallel-group study; 1 yr.; staging; mild to moderate asthma</td>
<td>241; average age +/- SD: 9.3 +/- 2.4 yr. (6-14 yr.)</td>
<td>BDP 400 mcg/day or Salmeterol 100 mcg/day or placebo; dry powder with Diskhaler followed by rinsing, gargling with water and expectoration</td>
<td>BDP group: 3.96 cm growth; placebo group: 5.04 cm growth; Salmeterol: 5.4 cm growth.</td>
<td>ICS growth suppression activity is relatively short; there is a capacity to zero growth suppressing effect. Growth suppressing activity is not observed after 18 weeks of treatment</td>
</tr>
<tr>
<td>Doull et al. 1998</td>
<td>Randomized double-blind placebo-controlled study; 2-6-wk admission period; 7-wk. treatment; 4-mo. interval</td>
<td>50; age ?</td>
<td>BDP 400 mcg/day, dry powder, via Diskhaler</td>
<td>Growth of children receiving BDP was significantly delayed during weeks 0-6, and similar to predicted growth when not receiving CS during weeks 17-24 and 25-30</td>
<td>ICS growth suppression activity is relatively short; there is a capacity to zero growth suppressing effect. Growth suppressing activity is not observed after 18 weeks of treatment</td>
</tr>
<tr>
<td>Crowley et al. 1998</td>
<td>One-year study comparing BUD, BDP, ICS + prednisolone and treatment without corticoids; collagen markers and bone metabolism were assessed</td>
<td>56; 35 boys, 21 girls; average age 8.32 yr., DP +/- 2.06 yr.</td>
<td>BUD average yearly dose 762 mcg/m²/day, BDP 560 mcg/m²/day, some used spacers; twice-daily; prednisolone (doses varied)</td>
<td>Growth velocity delay</td>
<td>Reduced growth velocity in patients was not a result of age grouping of prepubescent patients, when there is a physiological decline in growth rate, or when poor control of symptoms may occur. Reduced growth velocity was attributed to the side effects of treatment</td>
</tr>
<tr>
<td>Heuck et al. 1998</td>
<td>Randomized double-blind crossover trial, two 4-week treatment courses; knemometry</td>
<td>24; age 5.6 – 12.5 yr.</td>
<td>BUD 800 mcg/day administered once daily in the morning, and BUD 400 mcg twice daily</td>
<td>Average leg growth rate decreased during twice-daily administration</td>
<td>When compared with BUD 400 mcg twice daily, BUD 800 mcg administered in a single dose in the morning has a saving effect on short-term growth suppression</td>
</tr>
</tbody>
</table>

Abbreviations: ICS: inhaled corticosteroids; TAA: triamcinolone acetonide; BDP: beclomethasone dipropionate; BUD: budesonide; FP: fluticasone propionate; SCG: sodium cromoglycate; yr.: year/years; mo.: month/months; wk.: week/weeks.

reported a 4-year follow-up of a cohort of 3,347 asthmatic patients 1 to 25 years old. The heights of 2,345 of these children were assessed. The children were classified according to severity of asthma, and only the group that needed hospitalization and received ICS doses higher than 400 mcg/day showed growth delay. It was not clear whether growth delay could be attributable to ICS therapy or to poorly controlled asthma. A recent 20-month randomized double-blind study compared the use of BDP and FP in childhood asthma. Twenty-three children (ages 5-10 years) with moderately severe asthma and not previously treated with corticosteroids received 400 mcg/day BDP or 200 mcg/day FP in sprays with a spacer. The FP group grew 5.75 cm/year on average, while the BDP group grew significantly...
### Table 2 - Studies reporting dose-dependent results

<table>
<thead>
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<tr>
<td>Bisgaard 199319</td>
<td>Randomized single-blind crossover trial; 3 consecutive wk - treatment courses, no interval; manual knemometry</td>
<td>18; average age 27 mo. (13-36 mo.)</td>
<td>BUD 200 mcg and 800 mcg/day, inhaler with spacer and facial mask</td>
<td>BUD 800 mcg/day affected short-term growth, which was not observed for 200 mcg/day</td>
<td>Measurements may reflect systemic activity of cs, but probably do not indicate long-term changes in height</td>
</tr>
<tr>
<td>Agertoft &amp; Pedersen 199420</td>
<td>Controlled prospective study; admission period: 1-2 yr.; treatment: 3-6 yr.; stadiometry; mild to moderate asthma</td>
<td>216; 62 controls; average age 6.2 yr. (3-11 yr.)</td>
<td>Average BUD 700 mcg/day (initially) to 400 mcg/day (in the end of treatment); Nebuhaler with spacer or Turbuhaler (powder)</td>
<td>High doses of BUD (approx. 800 mcg/day) were associated with significant reduction of stature SD; daily doses &lt; or = 400 mcg/day did not adversely affect growth velocity</td>
<td>The dose required for asthma control decreased during the study without any loss of asthma control</td>
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<tr>
<td>Whitaker et al. (letter) 199621</td>
<td>Of a group of 66 children, the 20 with the lowest growth rate were changed to FP for 1 yr.; not many details</td>
<td>20; prepubescent children</td>
<td>FP 100-200 mcg/day</td>
<td>Growth “caught up”</td>
<td></td>
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<tr>
<td>Agertoft &amp; Pedersen 199722</td>
<td>Randomized double-blind placebo-controlled crossover study; treatment 15-18 days; knemometry twice/wk.; mild asthmatics; 3 treatment courses and 2 interval periods</td>
<td>48; average age 9 yr. (6-12 yr.)</td>
<td>FP 200 mcg/day, FP 400 mcg/day - dry powder, via Diskhaler; BUD 200 mcg/day, dry powder, via Turbuhaler</td>
<td>Leg-growth rates were similar during placebo treatment, FP 200 mcg/day and BUD 200 mcg/day, and lower with FP 400 mcg/day and BUD 400 mcg/day, but difference was significant only for BUD vs. placebo</td>
<td>A significant reduction in leg-growth rate in a knemometry study cannot be used to predict long-term adverse effects on growth</td>
</tr>
<tr>
<td>Barnes et al. (abstract) 199723</td>
<td>Open-label trial; 2 groups</td>
<td>32; ages 3-8 years</td>
<td>BDP or BUD 200-400 mcg/day - dry powder. After 1 yr., 16 children were changed to FP 100-200 mcg/day</td>
<td>Growth suppression in the first year. Growth “caught up” in group that changed to FP FP 200 mcg/day</td>
<td></td>
</tr>
<tr>
<td>de Benedictis et al. (abstract) 199824</td>
<td>Randomized double-blind study; 1 yr.; stadiometry</td>
<td>343; ages 4-11 yr.</td>
<td>FP 400 mcg/day or BDP 400 mcg/day, dry powder via Diskhaler</td>
<td>Growth velocity was higher for FP group than BDP group (4.99 cm/yr. vs. 4.09 cm/yr.)</td>
<td>Inhaled FP 400 mcg/day is effective and safe as treatment for asthmatic children who need relatively high ICS doses</td>
</tr>
<tr>
<td>McCowan et al. 199825</td>
<td>Four year follow-up of a cohort of children in Scotland; multi-center study; social-economic analysis</td>
<td>2,355; average age at final height measurement was 9.7 yr.</td>
<td>High ICS dose for phase 4 of treatment</td>
<td>Only children in phase 4 (high ICS dose) showed growth rate lower than rate for reference population and for other groups</td>
<td>Height reduction due to asthma is not simply the result of treatment, but the result of a complex interaction of factors, which may include level of asthma control and underlying severity of the disease</td>
</tr>
<tr>
<td>Rao et al. 199926</td>
<td>Randomized prospective double-blind study of children not previously treated with ICS; moderately severe asthma; 20 mo.; stadiometry</td>
<td>23; 5-10 yr.</td>
<td>BDP 400 mcg/day, FP 200 mcg/day, both with spacer</td>
<td>FP group grew on average 5.75 cm/yr. (no difference between FP and placebo groups); BDP group grew significantly more slowly, at an average of 4.94 cm/yr.</td>
<td>Almost all children in BDP group showed decrease in stature SD during the last period of the study, which was notably absent in the FP group.</td>
</tr>
<tr>
<td>Ferguson et al. 199927</td>
<td>Randomized double-blind placebo parallel-group study; moderate to severe asthma; stadiometry; 2-wk. admission period, 2-wk. treatment period, and 2-wk. follow-up periods</td>
<td>166 in FP group, age 8.2 +/-2 yr.; 167 in BUD group, age 7.9 +/-2 yr.</td>
<td>FP 400 mcg/day, dry powder via Diskhaler; BUD 800 mcg/day dry powder, via Turbuhaler</td>
<td>Linear growth rate was lower in BUD group (average difference 6.2 mm)</td>
<td>The study was not designed to critically assess growth as a factor resulting from treatment; height assessment was not standardized, except for stadiometry in fewer than 50% of the children</td>
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</table>

**Abbreviations:** CS = corticosteroids; ICS = inhaled corticosteroids; BUD = budesonide; FP = fluticasone propionate; BDP = beclomethasone dipropionate; yr. = year; mo. = month; wk = week.
Table 3 - Retrospective studies and meta-analyses/ICS and growth

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<td>Allen et al. 1994⁸⁸</td>
<td>Meta-analysis of 21 studies</td>
<td>810</td>
<td>Oral CS and BDP (doses not reported)</td>
<td>There is no statistical evidence that BDP treatment is associated with growth delay or higher doses and/ or longer treatment, and/or more severe asthma</td>
<td>Delayed sexual development observed in many children with asthma may result in growth delay when compared with control children</td>
</tr>
<tr>
<td>Silverstein et al. 1997⁹⁹</td>
<td>Retrospective cohort study to compare adult height attained in asthmatic patients</td>
<td>153; average age at asthma onset: 5.2 yr.; average age at first exposure to glucocorticoid: 12.5 +/- 3.9 yr.; age at measurement of adult height: 25.7 +/- 5.2 yr.</td>
<td>ICS, oral and parenteral corticosteroids (doses not specified)</td>
<td>Asthma patients' height was not significantly different from non-asthmatic patients' height; those who received glucocorticoids attained an adult height not significantly different from those who did not</td>
<td>Adult height of asthma patients that received only ICS was 0.9 cm shorter than height of asthma patients that were not treated with glucocorticoids</td>
</tr>
<tr>
<td>Van Bever et al. 1999⁹⁰</td>
<td>Retrospective study; adult height was checked for young adult asthmatic patients treated with ICS in childhood, and compared with height of asthma patients never treated with ICS; stadiometry</td>
<td>85</td>
<td>The majority received BDP; a few received BUD; spacing device; doses not specified</td>
<td>Those that received ICS in childhood showed a statistically significant smaller value of adult height minus expected height than those that never received ICS</td>
<td>The differences detected in adult height minus expected height between the 2 groups may be a consequence of asthma severity, and not only of ICS use</td>
</tr>
<tr>
<td>Lipworth 1999⁹¹</td>
<td>Systematic literature review and meta-analysis</td>
<td>Not reported</td>
<td>ICS (not specified)</td>
<td>There is no evidence to support any significant effect on final adult height</td>
<td>Short-term knemometry does not predict effects on long-term growth; intermediate-term growth study results may not predict the</td>
</tr>
<tr>
<td>Inoue et al. 1999⁹²</td>
<td>Retrospective study of long-term BDP treatment and height during puberty and final height; moderate to severe asthma; yearly height measured with stadiometry</td>
<td>97; 49 boys, 48 girls, age at beginning of treatment: 6-17 yr.</td>
<td>Average daily dose: BDP 300-800 mcg, with inhaler</td>
<td>Long-term inhaled BDP treatment in conventional doses does not significantly reduce linear growth and final height in asthmatic children</td>
<td></td>
</tr>
</tbody>
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Abbreviations: ICS - Inhaled corticosteroids; BDP - Beclomethasone dipropionate; BUD - Budesonide; yr. - year.

more slowly, at an average rate of 4.94 cm/year. The authors recognize that these findings do not necessarily mean long-term decreased final growth.

Table 3 presents meta-analyses and retrospective studies of the ICS effect on growth. Allen et al.⁸⁸ published a meta-analysis of 21 studies on the effect of oral corticosteroids and ICS on the growth of 810 patients. The studies included reported the exact number of asthmatic patients receiving corticosteroids who were the height predicted for their age or taller, and the exact number of asthmatic patients on corticosteroids who were below predicted height for their age. They tested the correlation between the use of corticosteroids and growth. The specific corticosteroid used in each study was classified in one of three analytical categories: 1) BDP (12 studies); 2) prednisone (8 studies); or 3) “other” oral corticosteroids (11 studies). The BDP
studies were analyzed for patient age (years), length of therapy (years), dose (mcg/day), and severity of asthma. BDP doses ranged from 400 mcg/day or less (8 studies) to more than 400 mcg/day (4 studies). Statistical analysis showed that BDP treatment resulted in a moderate but significant association with normal height when used in doses lower than 800 mcg/day. An apparent delay in growth was attributed to late puberty.

Lipworth,\(^9\) in a recent systematic review and meta-analysis of studies on ICS and their side effects, from 1966 to July 1988, did not find evidence to support any significant effect of BDP when used in daily doses lower than 400 mcg/day. His meta-analysis covered several ICS side effects, while growth was reviewed systematically only in studies of use of FP, BDP, BUD and oral prednisone. He concluded that the suppression of asthma effects in children is usually more important than any ICS systemic bioactivity that may impair long-term growth.

Silverstein et al.,\(^8\) in a retrospective cohort study, concluded that the use of ICS in the management of asthma is not associated with clinically significant effects on attained adult height. This study, however, was criticized\(^9\) on the premise that the average age of asthma onset for patients in the study was 6.1 years, and the average age of initial corticosteroid exposure was 12.5 years, when the average number of patients in the study was already over their growing years. Questions were also raised about the small number of patients and the cumulative dose of corticosteroids received, which was considered low when compared to doses presently in use.

A recently published study\(^9\) retrospectively analyzed the long-term effects of BDP treatment (average daily dose 300-800 mcg) on height during puberty and final height of asthmatic children. No evidence of growth delay was found when ICS was used. Another recent retrospective study observed growth delay in patients that received ICS in childhood when compared with the control group of asthmatic patients who did not receive ICS. The authors, however, attribute their findings to the differences in asthma severity in the two groups studied, and not only to the long-term use of ICS,\(^88\)\(^89\)\(^9\) which suggests that attained adult height is not affected by ICS use.

Conclusions

The use of ICS in childhood asthma does not seem to delay growth. Personal variations in drug absorption and metabolism make it clear that growth must be monitored for any child or adolescent receiving ICS, and that the minimum effective dose for good clinical control of asthma should be achieved. Concurrently, it is important to avoid the “corticosteroid phobia,” since uncontrolled asthma is detrimental not only to growth but also to quality of life, and may even be fatal. To quote Brook, “Short stature never killed anybody!”\(^4\)

References


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