

Review

Glucocorticoids and growth in asthmatic children

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The effects of asthma and oral and inhaled glucocorticoid therapy on growth in children are reviewed. Previous reports have shown that asthma itself may delay the onset of puberty, an effect which may masquerade as growth suppression. Oral glucocorticoids appear to impair growth; however, lower doses and alternate-day therapy may have less risk of this effect. While a controversial topic, inhaled glucocorticoids in lower doses appear to be associated with a small risk of adverse effects on growth. Minimal data are available for higher doses. Knemometry, a relatively new technique used for measuring small changes in growth, has detected short-term effects with both oral and inhaled glucocorticoids therapy. However, a number of limitations are associated with short-term growth studies. Clinicians should be aware of the potential for growth impairment with glucocorticoid therapy so adequate monitoring can be undertaken and appropriate intervention introduced when deemed necessary.

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Glucocorticoids represent a group of extremely potent anti-inflammatory agents and at the present time are highlighted as the treatment of choice for patients with persistent asthma (1–4). This review is focused on the potential impact of these therapies on growth in children. The discussion will begin with a review of pertinent information related to the effects of asthma itself on growth, followed by a discussion of the effects of systemic glucocorticoids. Since inhaled glucocorticoids are now a cornerstone of asthma therapy, the remainder of this discussion will summarize available information related to the potential impact of this treatment modality on growth in asthmatic children.

Asthma and growth

The hypothesis that asthma, as a chronic disease, might itself affect childhood growth has been a topic of discussion for many years. To answer this question we must rely on studies performed before the use of systemic and inhaled glucocorticoids. From a number of early observations prior to the popular use of glucocorticoids in the treatment of asthma, it appears that poorly controlled asthma and/or allergies affects growth in midchildhood and delays the onset of puberty, an effect which may present as

growth suppression. One early report demonstrated growth retardation in allergic children (5), a finding also observed in a subsequent study of allergic ($n = 66$) and asthmatic (36 of the 66) children, of whom 90% were below the mean height for age (6). It was later concluded that active allergy is a common cause of growth failure, but “growth repair” accompanies control of the allergy provided an adequate diet is available (7).

One study revealed 77% of steroid-naïve children with severe asthma to be below the normal age-related mean for height. Of these 30% were ≥ 1 SD below the mean and another 8% were ≥ 2 SD below the mean. In comparison, in another group of asthmatic children who had received intermittent or continuous glucocorticoid therapy, 15% and 33%, respectively, demonstrated heights ≥ 2 SD below the mean (8). Other trials have shown similar findings.

Seventy-four percent of asthmatic children were below the 50th percentile for height, with 27% below the 10th percentile in another investigation. Of note, these delays in growth were associated with delayed bone maturation (9), a finding confirmed in subsequent studies (6, 10). Another evaluation showed 37% of asthmatic children, all of whom had never received glucocorticoids, with height below the 25th percentile and 7% below the 3rd percentile.

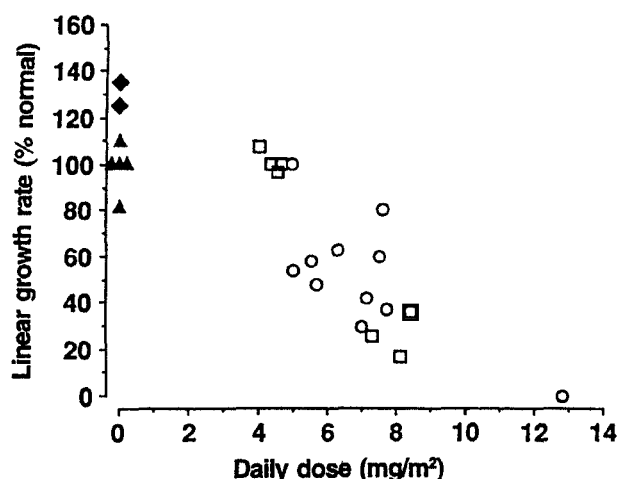


Fig. 1. Graph of linear growth rate vs. daily dose of systemic glucocorticoids. Open circles denote patients receiving prednisone and open squares denote those receiving methylprednisolone. Closed triangles denote patients observed prior to the onset of glucocorticoid therapy and closed diamonds those observed after cessation of treatment. Note reduced growth at doses > 5 $\text{mg}/\text{m}^2/\text{day}$, and that growth following discontinuation of glucocorticoid therapy is increased compared to normal. From reference 27.

Important factors related to the growth retardation observed were thought to be onset of asthma before 3 years of age, chronic hypoxemia, and poor appetite and milk intake (11). In a long-term investigation (mean follow-up 13.1 years), 66 children with perennial asthma (mean age 7.5 years upon entry) were studied. Final height measures were not affected; however, the onset of puberty was delayed by approximately 2 years for both females ($n = 19$) and males ($n = 47$) (12). This delay in the onset of puberty and lack of effect on final height has been confirmed in other studies (11, 13–16).

Several explanations for the association of asthma and delayed growth have been proposed (17).

1. *Asthma is associated with delayed maturation and a longer period of reduced growth rate prior to puberty.* While this might be seen as growth suppression, it does not compromise final height. This is consistent with findings from many studies.
2. *Growth hormone secretion is impaired.* This scenario does not appear likely as no objective evidence for such effects has been observed.
3. *Other endocrine malfunction.* Increased triiodothyronine concentrations were found in 7 of 16 asthmatic children with growth retardation (6); however, this was not supported by results from a subsequent study (19).
4. *Severity of asthma may influence growth.* In more severely asthmatic children, a high incidence of growth retardation has been observed (5, 7, 20–24), supporting this hypothesis. Further evidence

is the reported association of hypoxemia with growth retardation (11).

5. *Decreased appetite.* As with other systemic disorders, appetite may be affected by asthma; however, this was observed in early reports (11, 19) but was not confirmed in another (25).
6. *Increased energy demands.* Increased resting energy expenditure was observed in asthmatic children in one investigation (by 14% as compared to healthy, matched controls); however, other factors such as concomitant eczema or metabolic effects of β -adrenergic agonists might have contributed to this effect (25).

Fortunately, some studies have shown a “rebound” acceleration of growth rate or “catch-up” growth towards adulthood (10, 12). This, along with the delay in growth observed in some studies (as opposed to suppression), might account for the lack of effect on final height measures. Clearly, our understanding of the effects of asthma on growth in children is incomplete. Nevertheless, asthma does appear to have the potential to impair or delay growth in children. This must be considered when evaluating the effects of asthma medications, e.g., glucocorticoids, on growth.

Systemic glucocorticoids

The effects of systemically administered glucocorticoids on growth are now well known. A number of early case reports and studies have demonstrated that prolonged therapy with oral glucocorticoids can suppress growth.

One report demonstrated growth suppression with doses of hydrocortisone > 50 mg/m^2 body surface area per day. Following discontinuation of the glucocorticoid, however, growth rates were enhanced (26). Another study showed significant growth suppression with orally administered prednisone and methylprednisolone. Further analysis revealed that growth retardation was evident when the average dose exceeded 5 $\text{mg}/\text{m}^2/\text{day}$ for 6 months or longer, with essentially normal growth below this threshold (Fig. 1). The degree of suppression was roughly proportional to the dose and there were no differences between the different glucocorticoids (prednisone and methylprednisolone). As in the previous report, an acceleration of linear growth was observed after therapy was discontinued (27).

In a subsequent study, continuous glucocorticoids, but not intermittent therapy, were associated with significantly reduced linear growth. A similar prednisone threshold of 6 $\text{mg}/\text{m}^2/\text{day}$, above which effects on growth were evident, was observed (21). For asthmatic children who are already growth suppressed, more delay has been attributed to gluco-

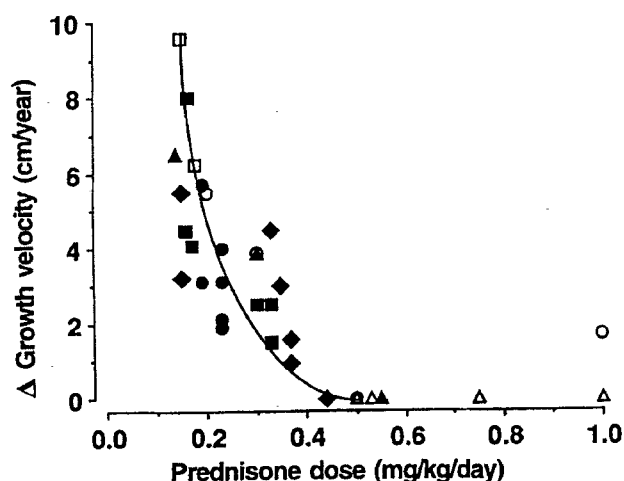


Fig. 2. Graph of the change in growth velocity while receiving treatment with growth hormone vs. prednisone dose. Symbols denote different observations for individual patients. Note lack of growth at doses >0.35 mg/kg/day. From reference 37.

coricoid therapy (15, 28), with the severity of increased retardation correlated to the dose and duration of glucocorticoid treatment (28). Finally, in a recent metaanalysis of previous investigations, a significant, albeit weak, growth impairment was found with prednisone and other oral glucocorticoids (29).

Alternate-day dosing has been suggested as a means to minimize the effects of glucocorticoids on growth (30–32). This was demonstrated in one report where children were treated for nephrotic syndrome, ulcerative colitis, and asthma with ≥ 30 mg every other day (41.8 ± 3.9 mg/day, mean $\pm$ SEM; range 30–60) for 6–50 months, yet had no untoward adverse effects, including growth suppression (31). In another study, alternate-day dosing of prednisone up to 14 mg was associated with accelerated growth of asthmatic children, whereas with higher doses (18–58 mg) growth suppression was observed. Of note, “catch-up” growth was not seen when patients with existing growth suppression (“height age” retardation of 1.4 ± 1.2 years, mean $\pm$ SD) were switched from daily to alternate-day (mean dose 17 mg every other day) prednisone (32).

Another method for increasing growth in children who require systemic glucocorticoids is therapy with growth hormone (33–37). It was recently demonstrated, however, that this therapy is only successful with prednisone doses <0.35 mg/kg/day (Fig. 2) (37). Substituting ACTH for prolonged glucocorticoid therapy has also been suggested for decreased effects on growth. In a series of cases, administration of ACTH was reported to allow for tapering of oral glucocorticoid doses with acceleration of growth velocity (difference of 0.37 cm/month between oral prednisone/prednisolone and ACTH treatments, $p < 0.001$) (38).

While our understanding of the effects of systemic glucocorticoids on growth in children is not complete, previous experience allows the following recommendations to minimize this adverse effect when therapy must be instituted:

1. Obviously, using the lowest possible dose is desirable. Intermittent therapy appears to be safer than continuous daily dosing (21). Prednisone and methylprednisolone doses less than 5–6 mg/m²/day do not appear to impede normal growth (21, 27).
2. Alternate day therapy may pose less risk of growth suppression. However, when higher alternate-day doses are used, with those exceeding ~ 15 mg of prednisone every other day there may be no less risk of impaired growth than with daily therapy (32).
3. Catch-up growth may be observed following discontinuation of therapy. This has been observed in some studies (30, 31), but was not seen when asthmatic children were switched from daily to alternate-day dosing (32).
4. If daily dosing is required and significant growth suppression is evident, other modalities to reduce the effects of systemic glucocorticoid therapy on growth may be necessary. Growth hormone has been shown to be useful (33–37), however, its efficacy may be limited by the dose of prednisone used (37).

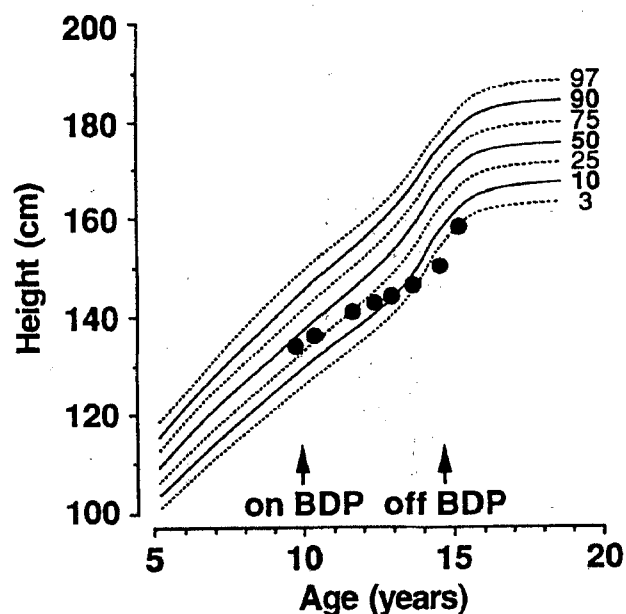


Fig. 3. Graph of height vs. age. Lines denote longitudinal standards. Note declining height percentiles after initiation of inhaled beclomethasone dipropionate (BDP) and increasing height percentiles following discontinuation of treatment. From reference 41.

Table 1. Significant differences in growth observed during a 1-year clinical trial comparing beclomethasone dipropionate (BDP) 336 µg/day and theophylline. Data from reference 50

Population/parameter	BDP	Theophylline	p value
Overall sample			
mean change between baseline and 6 months	2.2 cm	2.8 cm	0.016
mean change between baseline and 12 months	4.4 cm	6.0 cm	0.001
mean change between 6 and 12 months	2.2 cm	3.1 cm	0.015
mean growth velocity	4.2 cm/year	5.5 cm/year	0.005
difference between observed and predicted growth velocities	-0.7 cm/year	0.4 cm/year	0.001
Males overall			
mean growth velocity, baseline and 6 months	2.4 cm/6 mos	3.3 cm/6 mos	0.007
mean growth velocity, baseline and 12 months	4.8 cm/6 mos	6.5 cm/6 mos	0.002
mean growth velocity	4.5 cm/year	6.1 cm/year	0.007
difference between observed and predicted growth velocities	-1.0 cm/year	0.5 cm/year	<0.001
Males, pubescent			
difference between observed and predicted growth velocities	-1.0 cm/year	0.3 cm/year	0.015
Males, prepubescent			
mean growth velocity	4.3 cm/year	6.2 cm/year	0.005
difference between observed and predicted growth velocities	-1.0 cm/year	0.9 cm/year	0.004

Inhaled glucocorticoids

The potential for adverse effects on growth with inhaled glucocorticoid therapy has been the topic of much discussion and remains controversial. Growth retardation attributed to inhaled glucocorticoid therapy has been described in a limited number of case reports. In a series of cases of children aged 11 months to 16 years who had received 200–800 µg/day of beclomethasone dipropionate, modest reductions of height:age ratios and increases of weight:height ratios were observed (39). A case of overt glucocorticoid excess with triamcinolone acetonide 600 µg/day following a 5-day course of 5 mg prednisone three times daily has been reported. The 8-year-old girl described had no growth during the 6 months of treatment, but gained 3 cm in height over 4 months following discontinuation (40). Other cases of growth delay or suppression, typically described as decreasing growth percentiles, have been described with doses of beclomethasone dipropionate as low as 400 µg daily (Fig. 3) (41, 42).

Numerous studies have attempted to clarify the potential for growth impairment secondary to inhaled glucocorticoid therapy. Unfortunately, most investigations are limited by the low doses administered, relatively short length of follow-up, or use of previous or concurrent systemic glucocorticoids for asthma exacerbations. Also, the majority of investigations have been performed using beclomethasone dipropionate or budesonide, with minimal data available for the other inhaled glucocorticoids, specifically triamcinolone acetonide, flunisolide, and fluticasone propionate.

An early trial demonstrated no effects on growth with beclomethasone dipropionate 100–800 µg/day over ≥13 months of follow-up. Measured growth

during the year of treatment was 4.9 ± 1.3 cm (mean + SD) compared to expected growth of 5.0 ± 0.9 cm. Confounding the data, however, is that 18 of the 26 children studied were weaned off oral glucocorticoids during the first two months of the study. Thus, it is unclear whether growth acceleration after discontinuation of systemic glucocorticoid therapy may have affected the outcome. Also, 15 children required oral therapy for exacerbations at some point of the study (43). In another investigation, 7 prepubertal children (4 boys, 3 girls; ages 9 years, 1 month to 11 years) receiving a low dose of beclomethasone dipropionate (300 µg/day) for 18 months showed no untoward effects on growth or skeletal maturation (44).

With a slightly higher dose of beclomethasone dipropionate (532 ± 208 µg/day, mean ± SD), no changes in height percentiles were observed over 2.1 years of follow-up, as in prednisone-treated asthmatic children (29 ± 11 mg every other day). Height velocities, however, were reported to be skewed to lower percentiles for both groups ($39 \pm 6.6\%$ and $42 \pm 4.5\%$ for prednisone and beclomethasone dipropionate, respectively), and a trend toward inverse correlation of height velocities and glucocorticoid dosages (maintenance and daily therapy used as short courses for acute exacerbations) was observed (45). A prior trial of comparable dosages and durations (300–600 µg/day of beclomethasone dipropionate for up to 20 months) showed a similar lack of effect on growth. Interestingly, the substitution of systemic glucocorticoids for inhaled therapy was suggested to allow resumption of normal growth (46).

Longer studies of the effect of beclomethasone dipropionate on growth have been conducted. In a 16–40 month follow-up of 400 µg/day (with tapering

based on clinical response), no retardation of growth or skeletal maturation was observed. However, oral glucocorticoids were discontinued within the first 2 months of treatment in 6 of the 31 children studied (12 girls, 19 boys; ages 3.4 to 10.8 years). Of note, the boys deviated from the expected mean by +0.06 SD 12 months prior to the trial, -0.10 SD at the beginning of the observation period, -0.27 SD after one year, and -0.22 SD at the conclusion of the study. The girls, who showed more height deviation overall, did not change appreciably (-0.51 to -0.58 SD from the mean) throughout the study (47). In other long-term follow-ups, no effects on growth were seen with beclomethasone dipropionate 300-400 µg/day over 2.5-5 years of treatment (48, 49).

The aforementioned metaanalysis also examined the effects of beclomethasone dipropionate on growth. Interestingly, a significant moderate tendency for inhaled glucocorticoid treatment to be associated with *normal* stature was observed and there was no evidence of growth impairment with higher doses, longer durations of therapy, and more severe asthma (29).

A pivotal report which helped focus emphasis on the issue of growth suppression with inhaled glucocorticoids was a study sponsored by the American Academy of Allergy and Immunology. This investigation was a 1-year, multi-center, double-blind, double-placebo, randomized trial comparing theophylline and beclomethasone dipropionate (336 µg/day) in 195 children (aged 6 to 17 years) with mild to moderate asthma. Growth was extensively analyzed, and demonstrated suppressed growth velocity in the inhaled glucocorticoid-treated group (45 female, 57 male), particularly in male subjects (significant differences between groups in Table 1). No differences were seen in female subjects overall, prepubescent, or pubescent. This study, however, was limited by a lack of preentrance growth information, a relatively low dose of beclomethasone dipropionate (used without a spacer), lack of intrastudy assessment of puberty status, use of systemic glucocorticoids when needed, and lack of assessment for "catch-up" growth. Of note, the effects on growth were of a magnitude not generally appreciated by the children or their parents (50).

Budesonide, an inhaled glucocorticoid thought by some to be more potent with less risk of adverse effects than other inhaled glucocorticoids due to its anti-inflammatory and pharmacokinetic properties, has also been studied for its potential effects on childhood growth. In a recent report, height velocities of children aged 4.5-7.4 years receiving budesonide 200-1100 µg/m²/day (via metered-dose inhaler with spacer) were not different from controls (mean height velocity SD score 0.11 with 95% CI from -0.38 to 0.60). A modest delay in bone age

was observed (mean bone age SD score -0.68 with 95% CI -1.05 to -0.31 with no child delayed more than 2 SD from the 50th percentile); however, this was not related to the glucocorticoid dose (51). These results are similar to a 1-year prospective, open trial of 200 µg/day budesonide (via metered-dose inhaler with spacer) in children aged 3.5-7 years. In this study, no effects on growth rate (dramatic deviation from normal growth curve) or skeletal maturation were observed (52).

Longer evaluations of inhaled budesonide have also been performed. In a 3-year study of 600 µg/day (via metered-dose inhaler without spacer) in adolescents (aged 13.0 ± 1.1 years, mean ± SD) growth overall was not different from asthmatic controls; however, boys demonstrated reduced growth rates (mean difference -0.70 cm/year, 95% confidence interval -1.62 to 0.22). This finding was reported to be consistent with the delay in puberty due to asthma (53). Another study utilizing a relatively low dose of 200 µg/day (via metered-dose inhaler with spacer) for 3-5 years showed no effects on growth of 2-7-year-old asthmatics, as no patients demonstrated a deviation from their normal growth curve. Bone age was less than chronological age for most children at the beginning of the study, but increased toward normal with treatment. Of note, the majority of male subjects (8 of 10) were below the 50th percentile for height throughout the follow-up period (54).

In a study conducted in asthmatics treated with 400-800 µg/day of budesonide for 3-6 years (148 boys, 68 girls; aged 3 to 11 years), no untoward effects on growth and no differences between 62 asthmatic controls (16 girls, 46 boys; aged 3 to 11 years) were observed; however, a trend toward a dose-dependent effect was seen. Also, during the study a number of children were switched from administration via metered-dose inhaler with spacer to the Turbuhaler®, a dry powder inhaler device (55). Whether this change made a difference is not known, although recent data indicate that the Turbuhaler device provides twice the pulmonary deposition of budesonide than a metered-dose inhaler without a spacer (56). The clinical implications of this are not clear; however, one study demonstrated that doses of budesonide may be halved with no deterioration in asthma control when children are switched from delivery via a metered-dose inhaler with a spacer to Turbuhaler (57).

Based on the studies available which have examined the effect of inhaled glucocorticoids on growth, the following principles are evident:

1. *Of lower doses of inhaled glucocorticoids, those ≤ 400 µg/day, appear to be associated with a low risk of growth suppression.*

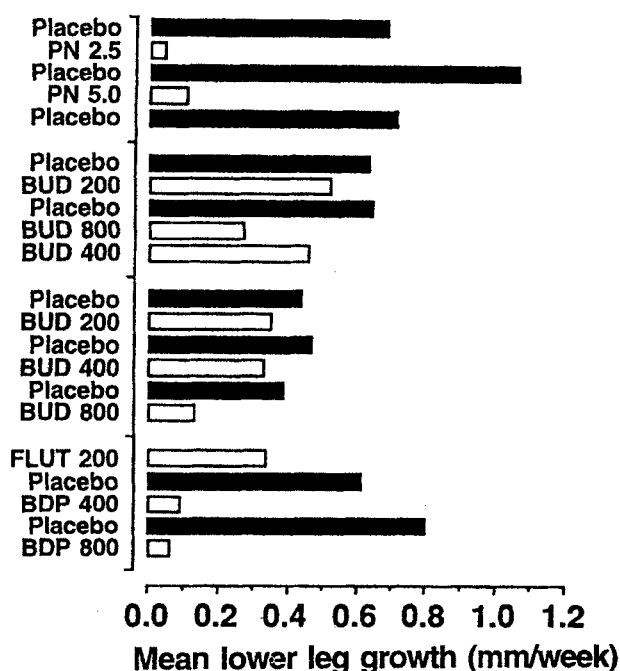


Fig. 4. Compilation of data demonstrating effects of oral and inhaled glucocorticoid therapy on short-term linear growth as measured by knemometry. PN = prednisolone, BUD = budesonide, FLUT = fluticasone propionate, and BDP = beclomethasone. Data from references 60, 62, 63, 65.

- Higher doses, > 400 µg/day, have not been well studied; however, a dose-dependent effect may exist.
- The effects of inhaled glucocorticoids on growth may have significant interpatient variability, as indicated by case reports. Also, data from which "equivalent" doses or relative potencies with regard to adverse effects could be derived are lacking.
- Resumption of normal growth following a switch from oral to inhaled therapy remains a possibility, but has not been well documented.
- Techniques to minimize systemic absorption, and the risk of growth impairment, are highly recommended. Available studies suggest that use of spacers and mouth rinsing following treatments reduce the systemic availability of inhaled glucocorticoids. Thus, these measures would appear to be logical steps to reduce the possibility of adverse effects of inhaled glucocorticoids on growth suppression.

Knemometry

In the past few years, linear growth has been extensively studied using a device known as a knemometer. This apparatus provides highly reproducible measurements of short-term (2–3 days) lower leg growth, with a precision of 0.2 mm and a coefficient of variation of 0.09% (58, 59). Using this technique,

the effects of systemic and topical (inhaled and intranasal) glucocorticoid therapies on short-term growth have been assessed (60–67), however; the major question of whether these measurements of short-term growth velocity predict long-term outcomes on growth remains to be elucidated.

An initial application of knemometry was to evaluate the effect of prednisolone on short-term growth of asthmatic children. Prepubertal children aged 7–11 years were administered 2.5 and 5.0 mg prednisolone daily for 2 weeks (divided into morning and evening doses), with run-in, placebo, and wash-out periods separating treatment periods. Significant reductions of growth velocities were observed with both treatments (Fig. 4). Growth rates were 0.04 ± 0.25 mm/week (mean $\pm$ SD) with 2.5 mg/day and 0.10 ± 0.21 mm/week with 5.0 mg/day, as compared to 0.68 ± 0.21 , 1.06 ± 0.83 , and 0.71 ± 0.35 mm/week during the run-in, placebo, and wash-out phases, respectively. Interestingly no catch-up growth was observed following discontinuation of treatment (60). In contrast, an evaluation of the growth of neonates treated with dexamethasone 0.2 mg/kg for 9 days showed a transient increase of growth rate following treatment. Mean lower leg growth was 0.367 mm/day 10 days prior to treatment, -0.003 mm/day during treatment, 0.518 mm/day 9–19 days after treatment, and 0.345 mm/day 20–40 days after treatment (61).

The effects of inhaled glucocorticoids have been examined using knemometry (Fig. 4). In a study of budesonide 200, 400, and 800 µg/day for 18 days (via metered-dose inhaler with spacer), a dose-dependent decrease of lower leg growth was observed. Growth rates were expressed as reductions; means were 0.11, 0.17, and 0.36 mm/week with the three treatments, respectively (62). Using a longer treatment period of 8 weeks each with the same three dosage levels, a significant reduction was seen only with 800 µg/day (by 0.26 mm/week). Actual growth rates were 0.35 ± 0.15 (mean $\pm$ SD), 0.33 ± 0.12 , and 0.13 ± 0.19 mm/week during the 200, 400, and 800 µg/day treatment periods, respectively. In contrast, growth velocities during placebo treatment ranged from 0.39 ± 0.15 to 0.47 ± 0.27 mm/week (63). In toddlers (mean age 27 months, range 13 to 36) receiving placebo or 200 or 800 µg/day of budesonide (via metered-dose inhaler with spacer and face-mask adapter) for 4 weeks, growth rates were 92 ± 69 (mean $\pm$ SD), 114 ± 62 , and 46 ± 70 µm/day, respectively (64).

The effects of beclomethasone dipropionate and fluticasone propionate on growth have also been studied using knemometry. With beclomethasone dipropionate in doses of 400 and 800 µg/day (via Diskhaler®, another dry powder inhaler), lower leg growth velocities were 0.09 ± 0.34 (mean $\pm$ SD) and

0.06 ± 0.21 mm/week, respectively. Growth with fluticasone propionate 200 µg/day (via Diskhaler) was also assessed, and was 0.34 ± 0.29 mm/week. In contrast, mean growths during the wash-out phases between treatments were 0.61 and 0.80 mm/week (65). As with Turbuhaler, inhaled drug delivery when administered via Diskhaler may be enhanced as compared to the conventional metered-dose inhaler. One study, using albuterol, demonstrated enhanced lung bioavailability with Diskhaler (68). Whether this holds true for inhaled glucocorticoids is not known; however, this change in delivery method may have influenced the results. Several precautions regarding the assessment of growth via knemometry and interpretation of short-term growth studies results have been noted (59, 69, 70), however. These include:

1. *There is a poor correlation between short- and long-term growth studies. Thus, short-term growth has little value in the prediction of final height* (69).
2. *Normal variations in growth, such as seasonal patterns and transient growth "spurts".* These can be large or small, and may further contribute to the limitations of short-term growth studies (69).
3. *Height velocity should be measured for at least 6 months before and after treatment* (58). *Catch-up growth may require longer intervals of observation* (69).
4. *Samples should be homogeneous and large enough to account for seasonal acceleration and annual variations of growth* (58). *Likewise, cyclical growth patterns require long study periods (6–12 months)* (70).
5. *The knemometer is more reliable for short-term studies than height, yet there is no support for using it during intervals shorter than 1–3 months.* It remains the current method of choice for short-term growth studies, however (69). The best use of knemometry appears to be in predicting potential growth retardation. Knemometry measurements should be made at the same time of day to allow for the leg-shrink phenomenon (59).
6. *The stadiometer remains the "gold standard" for measuring growth.* Three measurements at each session averaged to give the final height measurement are recommended (70). Measurements should be performed by no more than two or three trained observers (59).

Summary

Although high-dose, short-term glucocorticoid therapy is relatively safe in severe life-threatening disorders, chronic systemic glucocorticoid therapy has

significant risk of adverse effects. Topical formulations reduce the risk of adverse effects, but are not sufficient in many patients. As more aggressive use of glucocorticoid therapy, both inhaled and systemic, can be expected, the safety and efficacy of high-dose inhaled glucocorticoids must be evaluated along with continued development of glucocorticoids with improved topical potency. Until then, some general conclusions can be made:

1. *Asthma can be associated with a delayed onset of puberty, an effect which may masquerade as growth impairment.*
2. *Frequent use of systemic glucocorticoids can affect growth.* Doses of prednisone less than 5–6 mg/m²/day or alternate-day doses less than 15 mg every other day are desirable.
3. *Doses of inhaled glucocorticoids less than 400 µg/day, do not appear to impair growth.* However, the following precautions are warranted:
 - a. Individual patients may show alterations in growth velocity based on differences in absorption, elimination, or response to individual glucocorticoids. Individual monitoring is the only way to recognize these patients.
 - b. Incorporation of spacers and mouth rinsing techniques are highly recommended, especially if the glucocorticoid is readily absorbed from the oral cavity and gastrointestinal tract. A number of studies have shown the utility of spacers in alleviating the systemic adverse effects of inhaled glucocorticoids.
 - c. Newer inhaled delivery systems appear to have better pulmonary drug deposition (56, 68) and consequently greater absorption from the lungs. This may place the patient at risk of enhanced systemic effects, including growth impairment in children. Presumably, glucocorticoids with improved pharmacokinetic characteristics, such as budesonide and fluticasone propionate, could have less systemic effects than other agents.
4. *Doses of inhaled glucocorticoids greater than 400 µg/day may carry a dose-dependent risk of adverse effects on growth.* However, little information is available to substantiate this presumption. Once again, individual measurement of growth over extended periods of time, i.e., 6 months or longer, is necessary to identify susceptible patients. Appropriate monitoring techniques should be used.
5. *Effects on growth have been observed with inhaled glucocorticoid therapy.* If growth impairment is recognized, the following could be considered:

- a. Medications such as cromolyn sodium, nedocromil sodium, and perhaps theophylline, although potentially less effective than inhaled glucocorticoids, can be used as alternatives or supplements to inhaled glucocorticoids to reduce dosages and the risk of growth impairment.
- b. Another possibility is to substitute an alternative glucocorticoid, since there may be significant patient variability in systemic effects among the various inhaled glucocorticoids (71). The relative potencies of the different glucocorticoids, in terms of their risks for systemic adverse effects, are unclear, however. Also, minimal data are available with respect to flunisolide and triamcinolone acetonide.
- c. If the above interventions are not successful, evaluation by an endocrinologist and consideration of preventative therapy may be necessary.

Contrary to the opinion that physicians "should not be too worried about growth" since "short stature can be disadvantageous but is rarely fatal" (72), the adverse effects of inhaled, as well as systemic, glucocorticoids must be continually weighed against their beneficial effects in individual patients. Thus, dosing "as much as they [children] need to control their asthma" (73) may be inappropriate now that more agents are available and are being developed. Clinicians must be alert to the potential risk of adverse effects of medications, so that adequate monitoring and appropriate intervention can be undertaken when deemed necessary.

The asthma specialist can play a unique role in the health care system by ensuring optimal beneficial effects and minimal risk of adverse effects from the available medications, including inhaled glucocorticoids, and by teaching these principles to the primary care physician, who is responsible for the care of the large population of patients who fall into the mild to moderate categories of asthma severity.

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