

# THE JOURNAL OF Allergy AND Clinical Immunology

VOLUME 102

NUMBER 5

## Current reviews of allergy and clinical immunology

(Supported by a grant from Astra Pharmaceuticals, Westborough, Mass)

Series editor: Harold S. Nelson, MD

## Side effects of inhaled corticosteroids

John H. Toogood, MD, FRCPC *London, Ontario, Canada*

Inhaled corticosteroid (ICS) therapy carries less risk of complicating drug- or disease-related morbidity and mortality than that associated with other antiasthmatic drugs such as prednisone, theophylline, or  $\beta_2$ -agonist bronchodilators. Serious side effects are uncommon, but the risk increases with the daily dose. The degree of risk is most effectively minimized by ensuring each patient uses the smallest daily dose sufficient to maintain optimum control of their disease. Any patient in whom ocular symptoms develop while receiving ICS therapy should promptly be evaluated by an eye specialist. Growth velocity is commonly reduced during ICS therapy and should be monitored routinely. Bone metabolism may be affected by low or medium doses of ICS, but there is no evidence such doses cause osteoporosis or fracture. High-dose therapy may reduce bone density and increase the risk of fracture, particularly if other risk factors for osteoporosis are present. Research is needed to better define the impact of ICS therapy in children on height and peak bone density attained at maturity. Also, there is a need for practice guidelines specifically applicable to the prevention of bone loss during ICS treatment. (*J Allergy Clin Immunol* 1998;102:705-13.)

**Key words:** Asthma, inhaled steroids, side effects, adrenocortical suppression, cataract, glaucoma, growth, osteoporosis, infection, oropharynx complications, skin atrophy

The clinical indications for inhaled corticosteroid (ICS) therapy of asthma have broadened considerably over the past 20 years, and the advent of more potent drugs, more concentrated formulations, and more efficient delivery systems has greatly expanded its therapeutic potential. These changes also increase the likelihood of side effects, and this is a concern to parents, patients, and physicians. Some of these concerns are reviewed below; more comprehensive reviews have been published elsewhere.<sup>1,2</sup>

### Abbreviations used

|      |                                  |
|------|----------------------------------|
| BDP: | Beclomethasone dipropionate      |
| BMD: | Bone mineral density             |
| BUD: | Budesonide                       |
| DXA: | Dual energy X-ray absorptiometry |
| FP:  | Fluticasone propionate           |
| HPA: | Hypothalamic-pituitary-adrenal   |
| ICS: | Inhaled corticosteroid           |
| OS:  | Oral steroid                     |
| TA:  | Triamcinolone acetonide          |

## HYPOTHALAMIC-PITUITARY-ADRENAL AXIS EFFECTS Measurement

The impact of the systemically absorbed bioactive fraction of ICS on endogenous cortisol production may be assessed by a relatively insensitive test, such as the basal morning serum cortisol level, or by more sensitive tests, such as the 24-hour or overnight urinary free cortisol output, the 24-hour area under the curve of plasma cortisol, or the response to stimulating agents such as adrenocorticotrophic hormone. The sensitivity of the latter test is further increased if a low dose (0.5  $\mu$ g) is used.

Sensitive tests of hypothalamic-pituitary-adrenal (HPA) axis function have very limited efficiency for screening clinic populations to identify particular patients who may be at risk because abnormal values may be found in a majority of treated patients (Table I). Yet historically the incidence of complicating acute adrenocortical insufficiency has been extremely low.<sup>1</sup> In these circumstances higher predictive accuracy is attainable if a less sensitive diagnostic test is used in preference to a more sensitive test.

On the other hand, sensitive tests are preferred for studies that aim to accurately quantify and compare the pharmacodynamic activities of different ICS formulations for clinical research or regulatory purposes.

## Clinical effects

Anecdotal reports have been published of clinical hypercortisonism and/or a significant drop in cortisol pro-

From The London Health Sciences Centre, University Of Western Ontario, London.

Received for publication June 23, 1998; revised July 15, 1998; accepted for publication July 15, 1998.

Reprint requests: John H. Toogood, MD, FRCPC, Professor of Medicine, University Of Western Ontario, The London Health Sciences Centre, South Campus (Victoria), Allergy Clinic, 800 Commissioners Rd, East, London, Ontario, Canada N6A 4G5.

Copyright © 1998 by Mosby, Inc.

0091-6749/98 \$5.00 + 0 1/1/93404

**TABLE I.** Percent of group with subnormal values during a graded-dose BUD trial (n = 58)

| Response index for systemic ICS effect              | Daily dose (mg) |     |     |     |     |
|-----------------------------------------------------|-----------------|-----|-----|-----|-----|
|                                                     | 0*              | 0.4 | 0.8 | 1.6 | 2.4 |
| 8 AM serum cortisol <210 nmol/L (<7.6 µg/dL)        | 12*             | 14  | 19  | 19  | 24  |
| Urinary free cortisol <40 nmol/24 h (<1.45 µg/24 h) | 46*             | 57  | 73  | 80  | 80  |

All patients took each dose for 14 days in the left to right sequence shown. Data from J Allergy Clin Immunol 1995;96:157-66.

\*Subnormal values at baseline reflect carryover of the effects of the high-dose BUD or BDP (1.1 ± 0.4 mg/day) used by these patients with moderate-to-severe asthma before entering the study.

duction complicating the clinical use of low-dose beclomethasone dipropionate (BDP), triamcinolone acetonide (TA), budesonide (BUD), or fluticasone propionate (FP)<sup>3-6</sup> or high-dose BDP,<sup>7-9</sup> FP,<sup>10</sup> or TA, with the latter given at a dose of 3.0 to 9.0 mg/day by means of a nebulizer along with oral prednisone (see Appendix for description of the dose nomenclature used in this review.).<sup>11</sup> Accompanying adrenal atrophy or acute adrenocortical insufficiency has been documented in a few cases,<sup>11-13</sup> including one child ostensibly receiving a total nominal dose of 0.5 mg/day BUD for combined rhinitis and asthma treatment.<sup>5</sup> It is not clear whether such individuals metabolize glucocorticoids more slowly than normal, whether they use more than the prescribed dose, or perhaps both.

The cumulative dose of ICS may be an important determinant of its systemic effect on the HPA axis.<sup>7,14</sup> Although the evidence for this is limited, we observed, among a group of BUD-treated patients undergoing a systematic surveillance of the drug's long-term safety, a few individuals who tolerated high daily dosage for several years without adverse systemic effect but eventually dropped their morning cortisol significantly after the cumulative dose of BUD reached 1 g. One of these individuals experienced an episode of Addisonian crisis triggered by an acute enteric viral infection. These patients inhaled BUD (≥1.6 mg/day) by means of a spacer, and most required intermittent high-dose or alternate-morning low-dose prednisone as well.<sup>15</sup>

### Preventative action

Judged by the paucity of reported cases, stress-induced Addisonian crisis complicating ICS treatment appears to be rare. However, the fact that some patients may exhibit suppression of HPA axis function with low daily doses of ICS provides a clinical rationale for routinely administering a preventative glucocorticoid supplement to any patient receiving this treatment if they experience major trauma, surgery, or a severe prostrating illness.

It is more expeditious and less expensive to provide such prophylaxis routinely to all patients taking an ICS than to perform preliminary tests of HPA axis function in

an attempt to determine which patients are at risk for stress-induced Addisonian crisis. Others recommend such prophylaxis be restricted to patients who use high doses of BUD, BDP, or FP; those who use medium doses of TA; or those who have clinical features of hypercorticism. Lower threshold doses are recommended for children.<sup>14</sup>

There is no approved monitoring procedure to detect which ICS-treated patient may be at risk. It has been my practice to check the morning serum cortisol level once or twice a year in patients who require a dose of BDP or BUD of 1.6 mg/day or greater, especially if they require daily, alternate-day, or intermittent prednisone as well. However, the ideal monitoring technique for these circumstances remains controversial.

## OCULAR COMPLICATIONS

### Cataract

The pathogenesis of steroid-induced cataract may involve multiple mechanisms, including the formation of covalent adducts of the steroid molecule with the lysine residues of lens proteins.<sup>16,17</sup> The posterior subcapsular cataracts that result may partially or completely resolve after withdrawal of the drug, or they may progress despite withdrawal. Resolution of the cataract is consistent with the dynamic nature of these lesions.<sup>16</sup>

Most of the data relevant to this risk relate to BDP or BUD.<sup>18-20</sup> A large population-based survey found strong evidence that exposure to these drugs increased the prevalence of posterior subcapsular cataract about 2-fold, and the degree of risk was clearly related to both the current and cumulative lifetime dosages.<sup>18</sup> Evidence for a relationship to nuclear cataracts was suggestive but less strong.

On the other hand, cross-sectional surveys in asthmatic adults and children treated for long periods with relatively high doses of ICS indicate the risk of cataract is much less than with prednisone.<sup>19,20</sup> Cataracts have been observed to resolve after converting from oral prednisone to low-dose BDP.<sup>21</sup>

Opinions vary as to the advisability of routine ophthalmologic surveillance for cataract in patients treated with ICS. Cost-utility data are lacking. Ultimately, the mortality and morbidity risks associated with asthma take precedence over the risk of ocular complications. Where cataract does occur, it is correctable by surgery and there is no evidence that the efficacy of such surgery is dependent on or improved by early diagnosis.<sup>22</sup>

### Glaucoma

Anecdotal reports indicate that primary open-angle glaucoma may be exacerbated by antiasthmatic ICS, even at low dosage.<sup>23</sup> A large case-control survey found the risk increased significantly with high doses of BDP or BUD (above 1.5 mg/day; odds ratio: 1.44).<sup>24</sup> It did not increase with treatment duration or concomitant intranasal steroid use.

It is not known how the magnitude of this risk relates to the choice of drug, the inhalation procedure or delivery device used (eg, the open-mouth versus closed-mouth techniques with the pressurized metered dose inhaler),

individual patient susceptibility, or to interactions among these factors. Nebulized  $\beta$ -agonist and anticholinergic bronchodilators are known to increase intraocular pressure if deposited in the eye and topically absorbed.<sup>25</sup> This mechanism might apply in the case of ICS as well.<sup>22</sup>

## Management

In patients who have a personal or family history of glaucoma, it is prudent to measure intraocular pressure before or within a few days of commencing regular ICS therapy and then to monitor the pressure periodically. If the pressure rises, prompt treatment for glaucoma is indicated to avoid permanent impairment of vision.

Any patient in whom ocular symptoms develop while receiving ICS therapy should be evaluated promptly by an eye specialist.

## GROWTH

### Pathogenesis

Treatment with low-dose prednisolone or high-dose BUD (0.8 mg/day) suppresses the turnover of Type I collagen (localized mainly to bone) and Type III collagen (generally distributed throughout the body), and these changes are associated with growth inhibition.<sup>26,27</sup> BUD does not affect growth hormone secretion<sup>28</sup> or production of the insulin-like growth factor 1 or its major binding protein.<sup>26,27</sup> Presumably these findings apply to the other ICS drugs as well, but data are lacking.

### Clinical effects

Stunting has been observed in a few children treated with low- or high-dose BDP or BUD<sup>6,29,30</sup> or medium- or high-dose FP.<sup>3,10</sup> Controlled trials, using stadiometry or knemometry, document statistically significant reductions in growth rate in children treated with BUD greater than 0.4 mg/day<sup>31</sup> or BDP 0.4 mg/day or greater<sup>32,33</sup> but not with FP less than or equal to 0.2 mg/day.<sup>34</sup> In the latter study the possibility of a small drug effect on growth could not be definitely excluded. However, other studies that used the same dose of FP found no reduction in growth rate relative to control subjects treated with placebo<sup>35</sup> or cromolyn.<sup>36</sup> Furthermore, children whose growth rate had been observed to decline during treatment with BDP or BUD (0.2 to 0.4 mg/day) increased their growth rate after switching to a lower and equally effective antiasthmatic dose of FP (0.1 to 0.2 mg/day).<sup>37</sup>

In a study of asthmatic children (mean age, 4.4 years; range, 1 to 11 years) who grew normally before ICS treatment, growth retardation began soon after they commenced receiving BDP or BUD (0.14 to 2.0 mg/day).<sup>38</sup> This was evident with low and high doses, and between-subject differences in susceptibility were prominent. This emphasizes the importance of monitoring growth routinely, regardless of daily dosage.

### Dynamics and outcome

In children treated with 0.4 mg/day BDP, growth rate fell by 50% on average during the first 6 weeks of treat-

ment. Thereafter their growth rate paralleled that of untreated control subjects.<sup>32,39</sup> A compensatory period of “catch-up” growth did not occur during the 4 months after completing the BDP treatment.

However, such growth suppression may be offset eventually as evidenced by the only study that has prospectively followed BDP-treated asthmatic children through to adulthood; these children attained their predicted height.<sup>40</sup> Additionally, analyses of a large, population-based cohort found that asthmatic children treated with ICS or oral steroid (OS) reached normal adult height.<sup>41</sup> A limitation of these studies is that the exposure to ICS might have been different from that which applies currently. Larger doses, more potent drugs, more efficient drug delivery systems, and possibly the currently recommended use of repetitive bursts of high-dose ICS to treat asthma exacerbations might increase the degree of risk.

Thus it remains uncertain whether the reduction in growth velocity induced by ICS therapy may adversely affect the height attained in adulthood. Such studies are needed.

## BONE

Historically, osteoporosis and fracture have constituted the most common major complications of regular oral or parenteral steroid therapy for asthma. Therefore the possible effects of ICS on bone are of particular concern.

Most of the relevant literature relates to BUD, BDP, and to a lesser extent FP. Similar data are not available for flunisolide or TA.

### Bone turnover in adults

Bone formation may be inhibited and resorption increased by OS<sup>42-45</sup> or ICS<sup>42-50</sup> treatment. In general ICS drugs affect bone turnover less than therapeutically equivalent doses of OS as judged by graded-dose comparisons between BUD and prednisone.<sup>42,43</sup>

At milligram equivalent or therapeutically equivalent doses, respectively, BUD<sup>50,51</sup> and FP<sup>52</sup> affect bone metabolism less than BDP.

A reduction in bone resorption may accompany the primary reduction in bone formation induced by steroid treatment. This has been observed with low- or high-dose ICS and with low-dose OS therapy.<sup>42,44,46</sup> This downregulation of bone resorption acts to conserve the normal “coupling” between bone formation and resorption and thus diminish the likelihood of an adverse effect of the treatment on bone density.

### Bone density

Measurements of bone mineral density (BMD) provide the preferred basis for estimating the risk of fracture. A number of cross-sectional surveys have documented reduced bone mass in asthmatic adults receiving ICS therapy.<sup>53-55</sup> It is difficult to be sure of the causal role of the ICS in these studies because of uncertainties about confounding by past or current OS therapy or coexisting nonsteroidal risk factors for osteoporosis or inadequate matching for age and sex. However, several

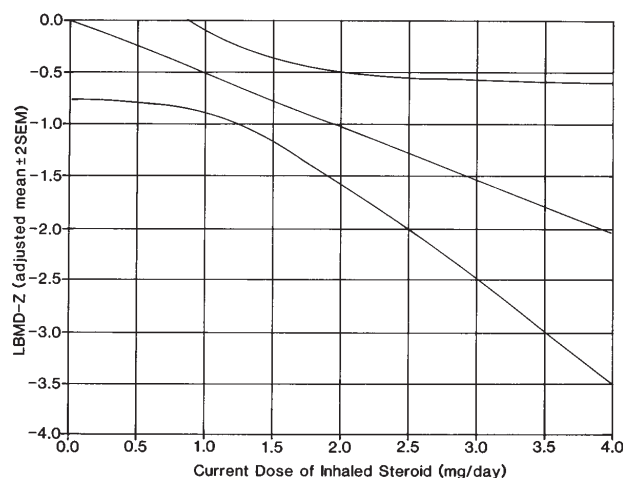


**FIG 1.** Regression of the lumbar spine BMD Z-score (LBMD-Z) on the daily dose of inhaled steroid. The values shown are adjusted to control for the effects of age, sex, years of estrogen use, physical activity, current daily dose of prednisone, years of prednisone use, and cumulative lifetime dose of inhaled steroid. The lumbar spine BMD Z-score declined significantly on the daily dose of inhaled steroid ( $P = .013$ , ANCOVA).<sup>57</sup>

cross-sectional surveys designed specifically to avoid or control for such potentially confounding factors found high-dose BDP or BUD therapy to be associated with bone depletion.<sup>56,57</sup>

In one of the latter studies, BMD declined by 0.5 standard deviations on average for each 1.0 mg increment in the daily dose of BDP or BUD (inhaled by means of a spacer) across an exceptionally broad range of dosage (0 to 3.2 mg/day;  $P = .013$ , ANCOVA).<sup>57</sup> The reduction in BMD was too small and variable to be statistically significant at doses lower than 1.0 mg/day but became significant as the dose increased above 1.0 mg (Fig 1). The postmenopausal women in the group, all of whom had received estrogen replacement therapy, conserved more normal BMD than the men when the sexes were compared at equivalent levels of exposure to ICS and OS.<sup>57,58</sup>

In addition to these cross-sectional surveys, a 2-year prospective study compared the effects on BMD of low to medium doses of BDP ( $0.63 \pm 0.25$  mg/day) with prednisone alone ( $12.0 \pm 5.0$  mg/day) in matched groups of asthmatic adults. In the regular prednisone group BMD declined about 8 times faster than normal, whereas in the BDP-treated group bone density declined normally.<sup>59</sup>

Another 2-year prospective study that compared asthmatic adults with healthy control subjects matched for age and sex found that BMD was not reduced by BUD or BDP (mean dose, 0.66 mg/day; range, 0.3 to 1.0 mg/day for an average of 10.6 years). Nor did these treatments accelerate the normal annual decline in bone density.<sup>60</sup> This applied also to the subset of postmenopausal women in the group, none of whom had received supplemental estrogen.<sup>60</sup>

Thus these prospective controlled studies establish that the effects that low or intermediate doses of BUD or BDP may manifest on bone metabolism are not, on average, indicative of significant bone depletion. However, no

prospective studies of bone mass have yet been reported in the patients most likely to be at risk (ie, the important minority who require ICS doses exceeding 1.0 mg/day).

Therefore there is a need for controlled prospective studies of bone density in patients who have a clinical need for high-dose therapy. Until such data become available, it is prudent to assume, on the basis of the significant associations identified in the above-mentioned cross-sectional studies, that bone may be depleted by nominal doses of BUD or BDP in excess of 1.0 mg/day or, presumably, by dose equivalents of the other ICS. This is especially true if the drug is inhaled by means of an efficient spacer or dry powder device known to increase intrapulmonary drug delivery.

## Fracture

No increase in the overall incidence of fracture has yet been reported in association with ICS therapy for asthma. One cross-sectional radiographic survey found vertebral fractures in 56% of a nonrandomly selected group of 25 asthmatic adults receiving regular prednisone ( $11.3 \pm 4.4$  mg/day). Significantly fewer fractures were found (8%,  $P = .02$ ) in a matched group treated with BDP ( $0.58 \pm 0.2$  mg/day).<sup>61</sup> Half the latter group received periodic short courses of prednisone as well.

Only 2 case reports of fracture complicating ICS therapy for asthma have been published to date.<sup>9,62</sup> These involved the administration of high-dose BDP (1.5 to 3.7 mg/day) for 2 or more years to adult male patients in whom the presence of major nonsteroidal risk factors for osteoporosis suggests that undiagnosed osteoporosis unrelated to steroid therapy might have been present at the time the ICS was started. The ICS therapy may have augmented the risk of fracture in these patients (see Table II for list of osteoporosis risk factors).

## Bone turnover in children

Short-term treatment with 0.2 to 0.8 mg BUD per day does not affect metabolic markers of bone formation or resorption.<sup>44</sup> However, longer treatment at similar dosages was associated with significant reductions in the metabolic processes of bone formation as evidenced by changes in osteocalcin and the carboxypropeptide of Type I procollagen.<sup>47</sup>

With respect to bone resorption, no increase in the urinary output of hydroxyproline or deoxypyridinoline has been observed with BUD doses up to 0.8 mg per day.<sup>44</sup> On the contrary, bone resorption was reduced in children receiving intermediate doses of BDP as evidenced by the serum level of tartrate-resistant acid phosphatase.<sup>63</sup>

BUD or BDP at a dosage of 0.8 mg/day,<sup>64</sup> or at dosages of 0.4 and 0.8 mg/m<sup>2</sup>/day,<sup>65</sup> did not perturb the normal "coupling" between bone formation and resorption, although they did inhibit bone formation. This would imply no increase in osteoporosis or the risk of fracture in these children, at least in the short term.

No data are available for children treated with higher doses of ICS, presumably because such doses are rarely used.

## Bone density

A cross-sectional survey of children treated with an intermediate dose of BDP for an average of 2 to 3 years found no reduction in BMD.<sup>63</sup> These patients were compared with asthmatic children not receiving ICS and also with healthy control subjects. Another cross-sectional pediatric study<sup>66</sup> found the BMD of 30 children receiving BDP at a dose averaging about 0.6 mg per day did not differ significantly from that of normal control subjects. Additionally, no correlations were found in these patients between BMD and the daily or lifetime cumulative dose of inhaled steroid. On the other hand, a recent cross-sectional survey found significantly lower total body BMD values in 40 asthmatic children treated with medium to high doses of BUD or BDP for 3 to 8 years in comparison with healthy control subjects.<sup>67</sup> Whether the difference was drug or disease related is unclear.

The largest cross-sectional survey of BMD reported to date compared 157 BUD-treated asthmatic children with 111 age-matched asthmatic control subjects. Three to 6 years of BUD at an average dosage of 0.5 mg/day (range, 0.19 to 1.3 mg/day) did not affect BMD, mineral capacity, or total bone calcium adversely.<sup>68</sup> None of these parameters correlated significantly with the current daily dose or accumulated lifetime dose or duration of BUD treatment.<sup>68</sup>

A prospective study of asthmatic children treated for at least 6 months with BDP (0.3 to 0.4 mg/day) found the mean bone density did not differ from that of age- and sex-matched asthmatic control subjects not treated with ICS.<sup>69</sup> However, the expected maturational increase in bone mass during a further 6-month treatment period was about 40% less in the BDP-treated patients than in the control subjects not receiving BDP. The clinical implications of this observation remain to be determined by longer follow-up.

**TABLE II.** Clinical risk factors for osteoporosis

|                                                     |
|-----------------------------------------------------|
| • Age greater than 60 years                         |
| • Postmenopausal state without estrogen replacement |
| • Male impotence or infertility                     |
| • Previous fractures with minor trauma              |
| • Parental history of fractures                     |
| • Past or current chronic glucocorticoid therapy    |
| • Smoking                                           |
| • Alcoholism                                        |
| • Physical inactivity                               |

Prepared from data from Arthritis Rheum 1996;39:1791-801.

## Long-term outcome

Longitudinal prospective studies are needed to determine the effect of ICS treatment on the peak bone mass attained at maturity. Because such data are lacking, it is not yet known how the early introduction of ICS therapy in children with mild asthma may affect their risk of osteoporosis in later years. Early introduction of ICS might conceivably reduce their future requirements for high-dose ICS, OS or both and thus reduce the risk of osteoporosis. On the other hand, if it should lead to a reduction in the peak bone mass attained during youth, this may be expected to increase the risk of osteoporosis later in life.

## Fracture

To date, there are no published surveys of fracture incidence or individual case reports of fracture complicating ICS therapy in asthmatic children.

## Prevention

There are no approved guidelines for preventing bone loss as it may relate particularly to ICS. The views summarized below are essentially empiric and they pertain to adults. There is a need for more formal guidelines that reflect the combined expertise of specialists in metabolic bone disease and asthma and are supported by prospective clinical studies that include cost-benefit assessments.

Currently available data indicate that all postmenopausal women starting ICS therapy should be offered estrogen replacement therapy because this may correct or prevent both steroid-induced and involutional osteoporosis.<sup>57,70,71</sup>

If an asthmatic patient with coexisting risk factors for osteoporosis as listed in Table II commences regular BDP, BUD, or FP therapy at a dose of greater than 1.0 mg/day (Higher threshold doses may apply for TA and flunisolide, but comparative systemic toxicity data are lacking.) it is prudent to prescribe an oral calcium supplement, obtain a baseline measurement of bone density by dual energy x-ray absorptiometry (DXA) as soon as convenient, and to recheck DXA after 1 year of treatment. Depending on the results of these tests, additional preventative or corrective antiosteoporosis therapy may be indicated. Supplemental calcium, estrogen, and/or bisphosphonate treatment are each known to be effective.<sup>72-76</sup> The feasibility of reducing the ICS daily dose should also be explored.

Patients whose maintenance dosage of ICS is known or appears likely to be 1 mg/day or less appear to be at little risk for osteoporosis. Therefore it is normally not necessary to measure bone density in such patients unless coexisting risk factors for osteoporosis are present.

However, if the patient or family express major concerns about the risk of osteoporosis, DXA may be clinically indicated to confirm the patient's low-risk status and facilitate adherence to the proposed long-term treatment plan. A systematic approach to the diagnosis and treatment of osteoporosis is summarized in several published algorithms.<sup>72,77</sup>

## INFECTIONS

### Immunologic effects

Prednisone 40 mg/day suppresses the plasma levels of IgG1, IgG2, and IgG3 subclasses.<sup>78</sup> At 10 mg/day it suppresses IgG3 only.<sup>78</sup> Unlike prednisone, exceptionally high doses of BUD (2.4 or 3.2 mg/day) administered by means of a high-efficiency spacer do not cause humoral immunosuppression.<sup>78,79</sup> Similar data are not available for the other ICS.

### Clinical effects

Increases in bacterial, viral, or fungal lung infections have not been a problem in patients treated with ICS in North America or Europe. A few cases of complicating pulmonary tuberculosis have been reported from India.<sup>80</sup> Prudence dictates that ICS be avoided or used with great caution in asthmatic patients who are immunosuppressed, who have coexisting drug-resistant or atypical tuberculosis, or who have structural lung lesions that may harbor a mycetoma. In the latter case, the risk of local immunosuppression leading to proliferation of locally resident pathogens and to locally invasive or disseminated disease is a concern, especially if ICS and OS are used conjointly.<sup>81</sup>

Although severe varicella has complicated the use of intranasal BDP for chronic sinusitis during the incubation phase of the disease,<sup>82</sup> the clinical course of varicella is not unduly severe or prolonged in asthmatic patients treated with ICS.<sup>83</sup>

Nevertheless, because a fraction of each dose of the inhaled drug is systemically bioavailable, because patients vary widely in their susceptibility to the systemic activities of glucocorticoids, and because it is not known how the choice of drug, route of administration, daily dose, or duration of ICS treatment may affect the risk of these complications developing, physicians are cautioned to take appropriate preventative action in any patient who may be exposed to these infections while receiving steroid therapy.<sup>84,85</sup> Depending on the circumstances, this may include the use of varicella-zoster immune globulin, pooled gamma globulin, and/or temporary withdrawal from the oral and/or inhaled steroid.<sup>84,85</sup>

## LOCAL EFFECTS IN THE OROPHARYNX

### Clinical effects

Dysphonia and candidiasis complicating ICS therapy are both significantly influenced by the daily dose of

ICS.<sup>1</sup> Otherwise, their pathogenetic determinants are quite dissimilar.<sup>1</sup> Because the dysphonia is not caused by laryngeal candidiasis, it does not need, nor will it respond to, treatment with antifungal agents. Twice daily dosing significantly reduces the incidence of thrush in comparison with 4-times daily dosing.<sup>86</sup> In general these complications are easily avoided and easily treated in most cases. The risk of thrush or dysphonia appears negligible with twice daily BUD administered by means of the dry powder Turbuhaler, even at high dosage.<sup>87</sup>

## SKIN

### Pathogenesis

In vitro studies show skin fibroblasts to be about 100-fold more sensitive to the effects of BUD or BDP than fibroblasts from the human lung.<sup>88</sup> As little as six weeks' treatment with BUD (0.4 to 1.6 mg/d) can markedly reduce the synthesis of Types I and III collagen, the main collagens in skin.<sup>89</sup>

### Clinical effects

Skin atrophy has been documented in patients receiving BDP or BUD (1.0 to 2.2 mg/day)<sup>91</sup> but not in patients treated with doses less than 1.0 mg/day.<sup>90</sup> Over time, the skin atrophy may lead to clinically apparent ecchymoses ("steroid purpura"), lacerations caused by trivial trauma, and slow wound healing. Age and female sex increase the risk.<sup>90,91</sup> In a study of patients using BDP or BUD (0.8 to 2.0 mg/day), two thirds of whom were women, close to 50% of the group showed bruising on inspection, and this correlated with the degree of reduction in their HPA axis function.<sup>90</sup> Steroid purpura may also correlate significantly with losses in bone density.<sup>57</sup>

## DETERMINANTS OF SYSTEMIC TOXICITY

### Drug delivery

All of the antiasthmatic effect and most of the systemic activity of ICS reflects the fraction of each dose delivered to the lung. Therefore increases (or decreases) in the "respirable fraction" of drug and/or the efficiency of the delivery system inevitably increase (or decrease) both the antiasthmatic and systemic effects of the drug in tandem. Similarly, changes in the oropharyngeal deposition of ICS influence the incidence and severity of oropharyngeal complications.

Rinsing the mouth and expectorating can reduce the gastrointestinal contribution to the overall systemic availability of ICS by up to 15%. This is potentially useful in the case of BDP but of little or no practical importance with more rapidly metabolized ICS such as BUD or FP.

The major influence that different delivery systems may exert on the intrapulmonary and oral delivery of ICS has been extensively reviewed elsewhere.<sup>2,92</sup> In addition, the patient's inhalation technique may affect the intrapulmonary delivery and systemic availability of ICS by a factor of 2 or more. The anticipated changeover from chlorofluorocarbon to hydrofluorokane propellants will require patients using the BDP pressurized aerosol to reduce their daily dose by about 50% to 60% because the

physical properties of the hydrofluorokane aerosol increase the fraction of each dose that is delivered to the lung and therefore systemically available.

### Daily dose

The dose dependency of the important side effect of ICS therapy on bone is illustrated in Fig 1. These data provide a basis for designating 1 mg/day as a threshold dose demarcating "safe" from "risk-prone" doses of BUD (inhaled by means of a Nebuhaler spacer). This may be assumed to apply to the Turbuhaler dry powder device as well because a comparative study found the performance characteristics of the Turbuhaler to be essentially equivalent in adults to those of the Nebuhaler spacer.<sup>87</sup> In children the Turbuhaler may be more efficient than the spacer.<sup>93</sup> Similar threshold doses for FP are less well defined for other ICS but are assumed to be lower and higher for fluticasone and TA. Lower threshold doses are generally recommended for children.<sup>94</sup>

### Adjunct drugs

In patients who have severe asthma requiring high-dose ICS, cotreatment with a "steroid-sparing" adjunct along with low- or medium-dose ICS can provide an efficacious alternative.<sup>95-97</sup>

### REFERENCES

- Toogood JH. Complications of topical steroid therapy for asthma. *Am Rev Respir Dis* 1990;141:S89-96.
- Pedersen S, O'Byrne P. A comparison of the efficacy and safety of inhaled corticosteroids in asthma. *Allergy* 1997;52:1-34.
- Zimmerman B, Gold M, Wherrett D, Hanna AK. Adrenal suppression in two patients with asthma treated with low doses of the inhaled steroid fluticasone propionate. *J Allergy Clin Immunol* 1998;101:425-6.
- Hollman GA, Allen DB. Overt glucocorticoid excess due to inhaled corticosteroid therapy. *Pediatrics* 1988;81:452-5.
- Zwaan CM, Odink RJH, van De Waal HAD, Dankert-Robles JE, Bokma JA. Acute adrenal insufficiency after discontinuation of inhaled corticosteroid therapy. *Lancet* 1992;340:1289-90.
- Thomas BC, Stanhope R, Grant DB. Impaired growth in children with asthma during treatment with conventional doses of inhaled corticosteroids. *Acta Paediatr* 1994;83:196-9.
- Brown PH, Blundell G, Greening AP, et al. Hypothalamo-pituitary-adrenal axis suppression in asthmatics inhaling high dose corticosteroids. *Respir Med* 1991;85:501-10.
- Brown PH. Hypothalamo-pituitary-adrenal axis suppression in asthmatic adults taking high dose beclomethasone dipropionate. *Br J Clin Pract* 1992;46:102-4.
- Chalkley SM, Chisholm DJ. Cushing's Syndrome from an inhaled glucocorticoid. *Med J Aust* 1994;160:611-5.
- Todd G, Dunlop K, McNaboe J, Ryan ME, Carson D, Shields MD. Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate. *Lancet* 1996;348:27-9.
- Carrel AL, Lemanske RF, Allen DB. Hypoglycemia and cortisol deficiency associated with low-dose corticosteroid therapy for asthma. *Pediatrics* 1996;97:921-4.
- Wong J, Black P. Acute adrenal insufficiency associated with high dose inhaled steroids. *Br Med J* 1992;304:1415.
- Busuttill A. Adrenal atrophy at autopsy in two asthmatic children. *Am J Forensic Med Pathol* 1991;12:36-9.
- Dluhy RG. Clinical relevance of inhaled corticosteroids and HPA axis suppression. *J Allergy Clin Immunol* 1998;101:S447-50.
- Toogood JH, Josephson D, Dervish G, Toogood PB. Safety of long term budesonide (BUD) therapy. *Clin Invest Med* 1989;12(4):B5.
- Shun-Shin GA, Brown NP, Bron AJ, Sparrow JM. Dynamic nature of posterior subcapsular cataract. *Br J Ophthalmol* 1989;73:522-7.
- Chylack LT. Cataracts and inhaled corticosteroids. *N Engl J Med* 1997;337:46-8.
- Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997;337:8-14.
- Toogood JH, Markov AE, Baskerville J, Dyson C. Association of ocular cataracts with inhaled and oral steroid therapy during long-term treatment of asthma. *J Allergy Clin Immunol* 1993;91:571-9.
- Simons FER, Persaud MP, Gillespie CA, et al. Absence of posterior subcapsular cataracts in young patients treated with inhaled glucocorticoid. *Lancet* 1993;342:776-8.
- Rooklin AR, Lampert SI, Jaeger EA, McGeady SJ, Mansmann JHC. Posterior subcapsular cataracts in steroid-requiring asthmatic children. *J Allergy Clin Immunol* 1979;63:383-6.
- Cumming RG, Mitchell P. Cataracts and inhaled corticosteroids: prevalence, prevention and management. *Drug Safety*. In press.
- Dreyer EB. Inhaled steroid use and glaucoma. *N Engl J Med* 1993;329:1822.
- Garbe E, LeLorier J, Boivin J, Suissa S. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. *JAMA* 1997;277:722-7.
- Kalra L, Bone MF. The effect of nebulized bronchodilator therapy on intraocular pressures in patients with glaucoma. *Chest* 1988;93:739-41.
- Heuck C, Wolthers OD, Hansen M, Kollergup G. Short-term growth and collagen turnover in asthmatic adolescents treated with the inhaled glucocorticoid budesonide. *Steroids* 1997;62:659-64.
- Wolthers OD, Hansen M, Juul A, Nielsen HK, Pedersen S. Knemometry, urine cortisol excretion, and measures of the insulin-like growth factor axis and collagen turnover in children treated with inhaled glucocorticosteroids. *Pediatr Res* 1997;41:44-50.
- Crowley S, Hindmarsh PC, Matthews DR, Brook CGD. Growth and the growth hormone axis in prepubertal children with asthma. *J Pediatr* 1995;126:297-303.
- Littlewood JM, Johnson AW, Edwards PA, Littlewood AE. Growth retardation in asthmatic children treated with inhaled beclomethasone dipropionate. *Lancet* 1988;1:115-6.
- Wales JKH, Barnes ND, Swift PGF. Growth retardation in children on steroids for asthma. *Lancet* 1991;338:1535.
- Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373-81.
- Doull IJM, Freezer NJ, Holgate ST. Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *Am J Respir Crit Care Med* 1995;151:1715-9.
- Simons FER. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. *N Engl J Med* 1997;337:1659-65.
- Allen AB, Bronsky EA, LaForce CF, et al. Growth in asthmatic children treated with fluticasone propionate. *J Pediatr* 1998;132:472-7.
- Konig P, Ford L, Galant S, et al. A 1-year comparison of the effects of inhaled fluticasone propionate and placebo on growth in prepubescent children with asthma [abstract]. *Eur Respir J* 1996;9(suppl 23):294.
- Price JF, Russell G, Hindmarsh PC, et al. Growth during one year of treatment with fluticasone propionate or sodium cromoglycate in children with asthma. *Pediatr Pulmonol* 1997;24:178-86.
- Whitaker K, Webb J, Barnes J. Effect of fluticasone on growth in children with asthma. *Lancet* 1994;348:63-4.
- Saha M, Laippala P, Lenko HL. Growth of asthmatic children is slower during than before treatment with inhaled glucocorticoids. *Acta Paediatr* 1997;86:138-42.
- Doull IJM, Campbell MJ, Holgate ST. Duration of growth suppressive effects of regular inhaled corticosteroids. *Arch Dis Child* 1998;78:172-3.
- Balfour-Lynn L. Growth and childhood asthma. *Arch Dis Child* 1986;61:1049-55.
- Silverstein MD, Yunginger JW, Reed CE, et al. Attained adult height after childhood asthma: effect of glucocorticoid therapy. *J Allergy Clin Immunol* 1997;99:466-74.
- Jennings BH, Anderson K-E, Johansson S-A. Assessment of systemic effects of inhaled glucocorticoids: comparison of the effects of inhaled budesonide and oral prednisolone on adrenal function and markers of bone turnover. *Eur J Clin Pharmacol* 1991;40:77-82.
- Hodsman AB, Toogood JH, Jennings B, Fraher LJ, Baskerville JC. Dif-

- ferential effects of inhaled budesonide and oral prednisolone on serum osteocalcin. *J Clin Endocrinol Metab* 1991;72:530-40.
44. Wolthers OD, Riis BJ, Pedersen S. Bone turnover in asthmatic children treated with oral prednisolone or inhaled budesonide. *Pediatr Pulmonol* 1993;16:341-6.
  45. Markov AE, Toogood JH, Hodsman AB, Steer B, Fraher LJ. Differential effects of inhaled budesonide and oral prednisone on biochemical markers of skeletal and adrenal functions. *J Bone Miner Res* 1992;7:S97.
  46. Toogood JH, Jennings B, Hodsman AB, Baskerville J, Fraher LJ. Effects of dose and dosing schedule of inhaled budesonide on bone turnover. *J Allergy Clin Immunol* 1991;88:572-80.
  47. Sorva R, Turpeinen M, Juntunen-Backman K, Karonen SL, Sorva A. Effects of inhaled budesonide on serum markers of bone metabolism in children with asthma. *J Allergy Clin Immunol* 1992;90:808-15.
  48. Pouw EM, Prummel MF, Oosting H, Roos CM, Endert E. Beclomethasone inhalation decreases serum osteocalcin concentrations. *Br Med J* 1991;302:627-8.
  49. Puolijoki H, Lippo K, Herrala J, Salmi J, Tala E. Inhaled beclomethasone decreases serum osteocalcin in postmenopausal asthmatic women. *Bone* 1992;13:285-8.
  50. Jennings BH. A comparison of budesonide and beclomethasone dipropionate in healthy volunteers. In: *The assessment of systemic effects of inhaled glucocorticoids* [dissertation]. Lund, Sweden: University of Lund; 1990.
  51. Ali NJ, Capewell S, Ward MJ. Bone turnover during high dose inhaled corticosteroid treatment. *Thorax* 1991;46:160-4.
  52. Bootsma GP, Dekhuijzen PNR, Festen J, Mulder PGH, Swinkels LMJW, van Herwaarden CLA. Fluticasone propionate does not influence bone metabolism in contrast to beclomethasone dipropionate. *Am J Respir Crit Care Med* 1996;153:924-30.
  53. Reid DM, Nicoll JJ, Smith MA, Higgins B, Tothill P, Nuki G. Corticosteroids and bone mass in asthma: comparisons with rheumatoid arthritis and polymyalgia rheumatica. *Br Med J* 1986;293:1463-6.
  54. Packe GE, Douglas JG, McDonald AF, Robbins SP, Reid DM. Bone density in asthmatic patients taking high dose inhaled beclomethasone dipropionate and intermittent systemic corticosteroids. *Thorax* 1992;47:415-7.
  55. Stead RJ, Horsman A, Cooke NJ, Belchetz P. Bone mineral density in women taking inhaled corticosteroids [letter]. *Thorax* 1990;45:792.
  56. Hanania NA, Chapman KR, Sturtridge WC, Szalai JP, Kesten S. Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol* 1995;96:571-8.
  57. Toogood JH, Baskerville J, Markov AE, et al. Bone mineral density and the risk of fracture in patients receiving long-term inhaled steroid therapy for asthma. *J Allergy Clin Immunol* 1995;96:157-66.
  58. Toogood JH, Hodsman A, Baskerville J, Markov A. Vertebral bone mineral density (VBMD) among elderly men and women receiving long term inhaled (I-S) or oral steroids (O-S) for asthma [abstract]. *J Allergy Clin Immunol* 1995;95:310.
  59. Luengo M, Del Rio L, Guanabens N, Picado C. Long-term effect of oral and inhaled glucocorticoids on bone mass in chronic asthma. A two year follow-up study. *Eur Respir J* 1991;4:342s.
  60. Luengo M, Del Rio L, Pons F, Picado C. Bone mineral density in asthmatic patients treated with inhaled corticosteroids: a case-control study. *Eur Respir J* 1997;10:2110-3.
  61. Luengo M, Picado C, Piera C, et al. Intestinal calcium absorption and parathyroid hormone secretion in asthmatic patients on prolonged oral or inhaled steroid treatment. *Eur Respir J* 1991;4:441-4.
  62. Laroche M, Porteau L, Caron P, et al. Osteoporotic vertebral fractures in a man under high-dose inhaled glucocorticoid therapy. (A case-report with a review of the literature.) *Rev Rhum Engl Ed* 1997;64:267-70.
  63. Konig P, Hillman L, Cervantes C, et al. Bone metabolism in children with asthma treated with inhaled beclomethasone dipropionate. *J Pediatr* 1993;122:219-26.
  64. Birkebaek NH, Esberg G, Andersen K, Wolthers O, Hassager C. Bone and collagen turnover during treatment with inhaled dry powder budesonide and beclomethasone dipropionate. *Arch Dis Child* 1995;73:524-7.
  65. Sorva R, Tahtela R, Turpeinen M, et al. Changes in bone markers in children with asthma during inhaled budesonide and nedocromil treatments. *Acta Paediatr* 1996;85:1176-80.
  66. Kinberg KA, Hopp RJ, Biven RE, Gallagher JC. Bone mineral density in normal and asthmatic children. *J Allergy Clin Immunol* 1994;95:490-7.
  67. Boot AM, de Jongste JC, Verbeke AAPH, Pols HAP, de Muinck Keizer-Schrama SMPF. Bone mineral density and bone metabolism of prepubertal children with asthma after long-term treatment with inhaled corticosteroids. *Pediatr Pulmonol* 1997;24:379-84.
  68. Agertoft L, Pedersen S. Bone mineral density in children with asthma receiving long-term treatment with inhaled budesonide. *Am J Respir Crit Care Med* 1998;157:178-83.
  69. Baraldi E, Bollini MC, De Marchi A, Zacchello F. Effect of beclomethasone dipropionate on bone mineral content assessed by X-ray densitometry in asthmatic children: a longitudinal evaluation. *Eur Respir J* 1994;7:710-4.
  70. Lukert BP, Johnson BE, Robinson RG. Estrogen and progesterone replacement therapy reduces glucocorticoid-induced bone loss. *J Bone Miner Res* 1992;7:1063-9.
  71. Hall GM, Daniels M, Doyle DV, Spector TD. Effect of hormone replacement therapy on bone mass in rheumatoid arthritis patients treated with and without steroids. *Arthritis Rheum* 1994;37:1499-505.
  72. American College of Rheumatology Task Force on Osteoporosis Guidelines. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheum* 1996;39:1791-801.
  73. Adachi JD, Bensen WG, Brown J, et al. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *N Engl J Med* 1997;337:382-7.
  74. Reid IR. Preventing glucocorticoid-induced osteoporosis. *N Engl J Med* 1997;337:420-42.
  75. Wang WQ, Ip MSM, Tsang KWT, Lam KSL. Antiresorptive therapy in asthmatic patients receiving high-dose inhaled steroids: a prospective study for 18 months. *J Allergy Clin Immunol* 1998;101:445-50.
  76. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med* 1997;337:1641-7.
  77. Scientific Advisory Board, Osteoporosis Society of Canada. Clinical practice guidelines for the diagnosis and management of osteoporosis. *Can Med Assoc J* 1996;155:1113-33.
  78. Van Schoor J, Toogood JH, Pauwels RA. Differential effects of inhaled budesonide and oral prednisolone on serum immunoglobulin G and its subclasses in healthy adult volunteers. *Clin Exp Allergy* 1997;27:192-5.
  79. Van Schoor J, Toogood JH, Pauwels RA. Short courses of high-dose inhaled budesonide and serum IgG subclass levels in healthy volunteers. *J Allergy Clin Immunol* 1996;97:113-8.
  80. Shaikh WA. Pulmonary tuberculosis in patients treated with inhaled beclomethasone. *Allergy* 1992;47:327-30.
  81. Anderson CJ, Craig S, Bardana EFJ. Allergic bronchopulmonary aspergillosis and bilateral fungal balls terminating in disseminated aspergillosis. *J Allergy Clin Immunol* 1980;65:140-4.
  82. Abzug MJ, Cotton MF. Severe chickenpox after intranasal use of corticosteroids. *J Pediatr* 1993;123:577-9.
  83. Nursoy MA, Bakir M, Barlan IB, Basaran NM. The course of chickenpox in asthmatic children receiving inhaled budesonide. *Pediatr Infect Dis J* 1997;16:74-5.
  84. Harter J. FDA responds to AAAI regarding use of corticosteroids. *AAAI News & Notes* 1993;2:12-3.
  85. FDA. Corticosteroids/treatment of those exposed to chicken pox. *FDA Med Bull* 1991;3:21.
  86. Toogood JH, Jennings B, Baskerville J, Anderson J, Johansson S. Dosing regimen of budesonide and occurrence of oropharyngeal complications. *Eur J Respir Dis* 1984;65:35-44.
  87. Toogood JH, White FA, Baskerville JC, Fraher LJ, Jennings B. Comparison of the antiasthmatic, oropharyngeal, and systemic glucocorticoid effects of budesonide administered through a pressurized aerosol plus spacer or the Turbuhaler® dry powder inhaler. *J Allergy Clin Immunol* 1997;99:186-93.
  88. Sarnstrand B, Jeppsson A, Malmstrom A, Brattsand R. Effect of glucocorticoids on hyaluronic acid synthesis in vitro in human fibroblast-like cells from lung and skin. In: *Glucocorticoids, inflammation and bronchial hyperreactivity*. Hogg JC, Ellul-Micallef R, Brattsand R, editors. Amsterdam: Excerpta Medica; 1985. p. 157-66.
  89. Autio P, Karjalainen J, Risteli L, Risteli J, Kiistala U, Okarinen A. Effects of an inhaled steroid (budesonide) on skin collagen synthesis of asthma patients in vivo. *Am J Respir Crit Care Med* 1996;153:1172-5.
  90. Roy A, Leblanc L, Paquette H, et al. Skin bruising in asthmatic subjects treated with high doses of inhaled steroids: frequency and association with adrenal function. *Eur Respir J* 1996;9:226-31.
  91. Capewell S, Reynolds S, Shuttleworth D, Edwards C, Finlay AY. Purpura and dermal thinning associated with high dose inhaled corticosteroids. *Br Med J* 1990;300:1548-51.

92. Dolovich M. Changing delivery methods for obstructive lung diseases. *Curr Opin Pulmonol Med* 1997;3:177-89.
93. Agertoft L, Pedersen S. Importance of the inhalation device on the effect of budesonide. *Arch Dis Child* 1993;69:130-3.
94. National Asthma Education Program EP. Guidelines for the diagnosis and management of asthma. US Dept of Health and Human Services; 1997 July. NIH Publication No: 97-4051. p. 1-146.
95. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994;344:219-24.
96. Pauwels RA, Lofdahl C-G, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;337:1405-10.
97. Evans DJ, Taylor DA, Zetterstrom O, Chung F, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. *N Engl J Med* 1997;337:1412-8.

## APPENDIX.

### Comments on dose and dose categories

All doses cited in this review are expressed in terms of the "nominal" dosage. This signifies the amount of drug emitted from the dry powder inhaler or valve of the pressurized metered dose inhaler with each activation. It is not adjusted for losses that may occur within the delivery device or add-on spacer, if attached. The marginal doses used in this review to designate "low," "medium," and "high" dose categories in the text reflect current US use<sup>94</sup> and may not correspond with those adopted in some other jurisdictions.

## Your comprehensive reference to valuable research information...

**N**ow you can have easy access to research information with the five-year cumulative author and subject index to Volumes 87-96 of *The Journal of Allergy and Clinical Immunology*.

The Cumulative Index is your comprehensive reference guide, including a list of every article in the Journal from 1991 through 1995. All articles are indexed both by subject and by author.

The Cumulative Index features:

- Offset and bold Subject Headings that make searching for subject entries easier
- Subject Entries containing complete article title, author(s), year of publication, volume, and page
- Author Entries listing author(s), article title, author-to-author referral, year of publication, volume, and page

Order *The Journal Of Allergy and Clinical Immunology* Cumulative Index today!

**M** Mosby

**YES!** Please send me the Five-Year Cumulative Index to *The Journal of Allergy and Clinical Immunology* (1991-1995). I've indicated my method of payment below. All prices include shipping.

☐ \$55.00 U.S.    ☐ \$63.66 Canada\*    ☐ \$59.50 International

\*Includes Canadian GST.

Payment must accompany your order.

- ☐ Check enclosed (U.S. funds, payable to *The Journal of Allergy and Clinical Immunology*)
- ☐ Mastercard    ☐ Visa    ☐ Discover

Credit Card # \_\_\_\_\_ Exp. Date \_\_\_\_\_  
Signature \_\_\_\_\_

Name \_\_\_\_\_  
Institution \_\_\_\_\_  
Address \_\_\_\_\_  
City \_\_\_\_\_ State \_\_\_\_\_  
Zip \_\_\_\_\_ Country \_\_\_\_\_

**To order, just call**  
**1-800-453-4351**

Outside the U.S.: 314-453-4351  
Fax: 314-432-1158

**Or return coupon to:**  
**Mosby, Inc.**  
**Periodical Subscription Services**  
**11830 Westline Industrial Dr.**  
**St. Louis, MO 63146 U.S.A.**

J01976FZ