

Glucocorticoid-induced osteoporosis: An update on effects and management

Bjoern Buehring, MD,^{a,b,*} Ravi Viswanathan, MD,^{c,*} Neil Binkley, MD,^{a,b} and William Busse, MD^c Madison, Wis

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the JACI Web site: www.jacionline.org. The accompanying tests may only be submitted online at www.jacionline.org. Fax or other copies will not be accepted.

Date of Original Release: November 2013. Credit may be obtained for these courses until October 31, 2014.

Copyright Statement: Copyright © 2013-2014. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Bjoern Buehring, MD, Ravi Viswanathan, MD, Neil Binkley, MD, and William Busse, MD

Activity Objectives

1. To summarize the epidemiology and pathophysiology of glucocorticoid-induced osteoporosis (GIO) and the role of oral and inhaled corticosteroids in asthmatic adults and children.
2. To review the clinical effect of GIO therapies on bone health in children and adults.
3. To review the American College of Rheumatology (ACR) GIO guidelines, including diagnostic and therapeutic measures, to reduce the risk of glucocorticoid-induced fragility fractures.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial

Companies/Organizations: N. Binkley has consultant arrangements with Merck and Lilly and has received grants from Merck, Lilly, and Amgen. W. Busse is on the Merck Board; has received consultancy fees from Amgen, Novartis, GlaxoSmithKline, MedImmune, Genentech, Boston Scientific, and ICON; has received research support from the National Institutes of Health (NIH)/National Institutes of Allergy and Infectious Diseases and the NIH/National Heart, Lung, and Blood Institute; and has received royalties from Elsevier. The rest of the authors declare they have no relevant conflicts of interest.

Glucocorticoids remain a cornerstone of guideline-based management of persistent asthma and allergic diseases. Glucocorticoid-induced osteoporosis (GIO) is the most common iatrogenic cause of secondary osteoporosis and an issue of concern for physicians treating patients with inhaled or oral glucocorticoids either continuously or intermittently. Patients with GIO experience fragility fractures at better dual-energy x-ray absorptiometry T-scores than those with postmenopausal

or age-related osteoporosis. This might be explained, at least in part, by the effects of glucocorticoids not only on osteoclasts but also on osteoblasts and osteocytes. Effective options to detect and manage GIO exist, and a management algorithm has been published by the American College of Rheumatology to provide treatment guidance for clinicians. This review will summarize GIO epidemiology and pathophysiology and assess the role of inhaled and oral glucocorticoids in asthmatic adults and children, with particular emphasis on the effect of such therapies on bone health. Lastly, we will review the American College of Rheumatology GIO guidelines and discuss diagnostic and therapeutic strategies to mitigate the risk of GIO and fragility fractures. (*J Allergy Clin Immunol* 2013;132:1019-30.)

Key words: Glucocorticoid, inhaled and oral corticosteroid, asthma, growth, osteoporosis, bisphosphonates

From ^athe University of Wisconsin Osteoporosis Research Program, Division of Geriatrics and Gerontology, University of Wisconsin School of Medicine & Public Health; ^bGRECC, William S. Middleton Memorial Veterans Hospital, Madison; and ^cthe Department of Medicine, Section of Allergy, Pulmonary & Critical Care, University of Wisconsin School of Medicine & Public Health.

*These authors contributed equally to this manuscript and are joint first authors.

Received for publication August 2, 2013; revised August 30, 2013; accepted for publication August 30, 2013.

Corresponding author: Bjoern Buehring, MD, University of Wisconsin Osteoporosis Research Program, Section of Geriatrics and Gerontology, Department of Medicine, University of Wisconsin School of Medicine & Public Health, 2870 University Ave, Suite 100, Madison, WI 53705. E-mail: bbuehring@medicine.wisc.edu. Or: Ravi Viswanathan, MD, Division of Allergy, Pulmonary & Critical Care, Department of Medicine, University of Wisconsin School of Medicine & Public Health, H4/612 CSC, 600 Highland Ave, Madison, WI 53792. E-mail: rviswanathan@medicine.wisc.edu.

0091-6749/\$36.00

© 2013 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2013.08.040>

Abbreviations used

ACR:	American College of Rheumatology
AFF:	Atypical femur fracture
ASBMR:	American Society for Bone Mineral Research
BDP:	Beclomethasone dipropionate
BMD:	Bone mineral density
CAMP:	Childhood Asthma Management Program
DXA:	Dual-energy x-ray absorptiometry
FDA:	US Food and Drug Administration
GIO:	Glucocorticoid-induced osteoporosis
ICS:	Inhaled corticosteroid
LABA:	Long-acting β -agonist
OCS:	Oral corticosteroid
OR:	Odds ratio

outline the pathophysiology and epidemiology of GIO, summarize the literature on the effect of inhaled and oral glucocorticoids on bone health, and discuss the American College of Rheumatology (ACR) guidelines for GIO management² and the commentary on these guidelines by the American Society for Bone and Mineral Research (ASBMR).³

GIO is the most common form of iatrogenic osteoporosis and also the most common form of secondary osteoporosis⁴⁻⁷ but remains a complex and often confusing issue for clinicians not intimately involved with osteoporosis treatment. Fragility fractures, the negative consequence of osteoporosis, occur in 30% to 50% of patients taking long-term systemic glucocorticoids. Fracture risk increases markedly in the first 3 months after

glucocorticoid initiation and decreases after discontinuing glucocorticoid therapy, but the risk appears to never return to baseline. Hip fracture risk increases up to 7-fold and vertebral fracture risk increases up to 17-fold with treatment with prednisone equivalent doses of 10 to 12 mg/d for more than 3 months. Fracture risk appears to be increased with prednisone doses as small as 2.5 to 3 mg/d.⁴⁻¹¹ Vertebral fractures occur at higher bone mineral density (BMD) values in those receiving glucocorticoids compared with nontreated patients.⁸ Hip and vertebral fractures are associated with significant morbidity, reduced quality of life, mortality, and health care costs.¹²

Limited data are available on the prevalence of GIO and GIO-related fractures in children.¹³⁻²¹ The incidence of vertebral fractures in children with systemic autoimmune diseases receiving glucocorticoids was estimated to be 6% after 1 year of treatment.²² The relative fracture risk increases by approximately 30% but can be up to twice as high (humerus fractures) in children receiving glucocorticoids (>4 courses of glucocorticoids per year) compared with the general pediatric population.¹⁷ Thus, glucocorticoid therapy increases fracture risk in both adults and children and is of clinical interest and importance to physicians involved in the care of asthma and allergic diseases, in which glucocorticoid use is fundamental to treatment.

OSTEOPOROSIS OVERVIEW

Osteoporosis is defined as follows: a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, resulting in increased bone fragility and susceptibility to fracture. This definition highlights 4 important aspects. First, osteoporosis is systemic, affecting the

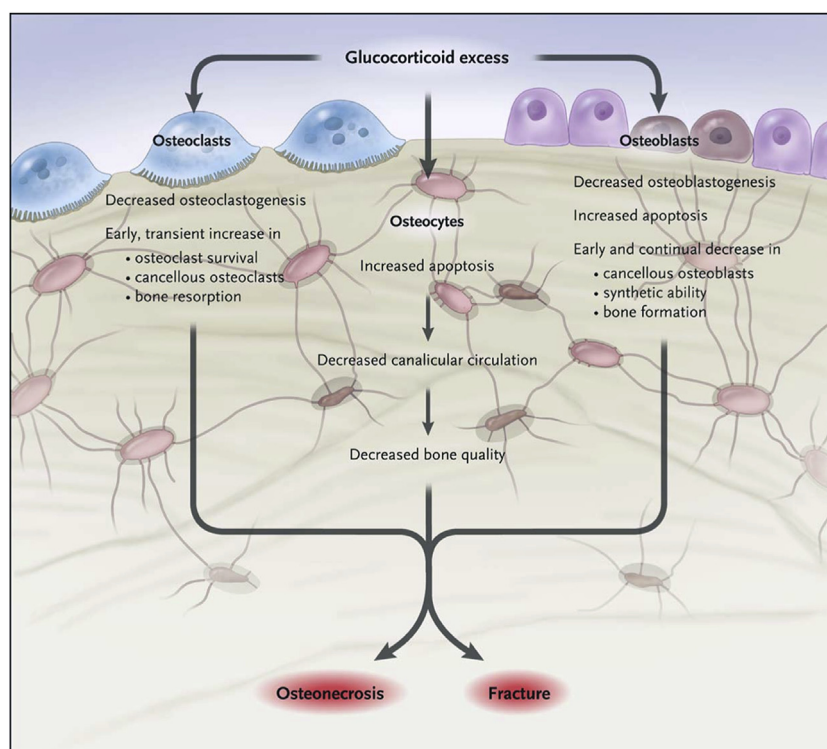


FIG 1. Direct effects of glucocorticoids on bone cells. Shown are the adverse skeletal changes that result from an excess of glucocorticoids and lead to osteoporosis and osteonecrosis. The *brown* condensed cells are apoptotic osteoblasts and osteocytes. Apoptotic osteocytes disrupt the osteocyte-lacunar-canalicular network. Reproduced with permission from Weinstein.⁷

TABLE I. Comparative daily dosages of ICSs

	Low daily dose child*/adult	Medium daily dose child*/adult	High daily dose child*/adult
BDP			
HFA MDI	80-160/80-240	>160-320/>240-480	>320/>480
BUD			
DPI	180-360/180-540	>360-720/>540-1080	>720/>1080
Nebules	500/UK	1000/UK	2000/UK
CIC			
HFA MDI	80-160/160-320	>160-320/>320-640	>320/>640
FP			
HFA MDI	88-176/88-264	176-352/264-440	>352/>440
DPIs	100-200/100-300	200-400/300-500	>400/>500
MF			
DPI	110/220	220-440/440	>440/>440

Reproduced with permission from Stoloff and Kelly.³⁹

BUD, Budesonide; CIC, ciclesonide; DPI, dry-powder inhaler; FP, fluticasone propionate; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; MF, mometasone furoate.

*Five to 11 years of age (except for budesonide nebulers: 2-11 years of age).

whole skeleton. Second, low bone mass or BMD is important but not the sole defining factor. Third, the loss of structural integrity known as microarchitectural deterioration is important to emphasize because approximately 50% of patients with fragility fractures do not have osteoporosis based on BMD (by using the World Health Organization T-score criteria of -2.5).²³ Finally, the health risk associated with osteoporosis is the fragility fracture. In the absence of fracture, osteoporosis is a “silent” disease and similar to hypercholesterolemia, with patients unaware of underlying poor bone quality. This concept is important in daily clinical care and when discussing osteoporosis with patients. It also explains why medications seeking regulatory approval for osteoporosis are required to demonstrate fracture risk reduction.

BONE ANATOMY AND PHYSIOLOGY

Bone is a multicomposite material that consists of cells (osteocytes, osteoblasts, and osteoclasts), extracellular organic components (collagen and noncollagenous matrix proteins), and nonorganic components (calcium hydroxyapatite). Bone strength/quality depends on all 3 factors. In adults, the body regionally adjusts bone geometry, thickness, density, and other parameters to meet forces that deform a particular bone.²⁴ Current research suggests that osteocytes are the main regulators of bone remodeling. These cells are thought to sense mechanical load and then stimulate or inhibit osteoclast and osteoblast activity. Osteoclasts are responsible for bone resorption, whereas osteoblasts are responsible for bone formation. Osteocytes also have the capacity to detect microdamage in bone and initiate bone repair in the damaged region, a process that occurs in all bone.²⁵ In patients with osteoporosis, abnormalities in regulation of osteocytes, osteoblasts, and osteoclasts lead to a net loss of bone strength/quality caused by changes in BMD, bone thickness, and geometry. Osteoporosis medications ultimately work by either altering osteoclast or osteoblast function.²⁶

Glucocorticoids adversely affect bone strength/quality in a number of ways.^{4,6,7,11,27} Notably, GIO is characterized by increased apoptosis of osteoblasts and osteocytes; decreased osteoblastogenesis, resulting in decreased bone formation; and disruption of bone remodeling regulation (Fig 1). Additionally,

after initiation of glucocorticoid therapy, there is an early and transient increase in bone resorption through enhanced osteoclast survival and osteoclastogenesis, which later changes to decreased osteoclastogenesis. The combination of increased bone resorption, decreased bone formation, and interruption of regulatory pathways explains, at least in part, the observations of an early and rapid loss of BMD and bone strength/quality in patients with GIO and also why fragility fractures occur at higher BMD values than in patients with non-GIO osteoporosis.^{8,11}

Glucocorticoids also adversely affect muscle function and mass by causing muscle catabolism through increased protein degradation and decreased protein synthesis. Muscle weakness is a well-known risk factor for increased balance problems and fall risk, which, in turn, increase the risk for fragility fractures.²⁸⁻³¹

GLUCOCORTICOID USE IN ASTHMATIC PATIENTS AND ITS EFFECT ON BONE HEALTH

Asthma is an inflammatory disease of the airways characterized by variable airflow obstruction, bronchial hyperresponsiveness, and heterogeneity in its clinical presentation, level of severity, and response to treatment. Although many therapies improve symptomatic manifestations of asthma, few treatments modify the underlying nature or course of the disease. For many patients, the pathophysiology and inflammation associated with asthma is determined by levels of T_H2 cytokines, the generation of which is often sensitive to glucocorticoids. Many biologic molecules, which target the various cytokine axes, particularly anti-IL-4 and anti-IL-13 (dupilumab),³² IL-5 (mepolizumab),^{33,34} IL-13 (lebrikizumab),³⁵ and IL-17 (brodalumab),³⁶ are being explored to improve asthma symptoms, prevent exacerbations, and produce disease-modifying effects to reduce the likelihood of side effects from glucocorticoids. Although these approaches have shown promise in some circumstances, other than omalizumab, mAbs have yet to be approved for general clinical use in asthmatic patients.

Consequently, glucocorticoids continue to be (and will remain so because of their effectiveness) a cornerstone of guideline-based management of persistent asthma. Glucocorticoids, particularly inhaled corticosteroids (ICSs), reduce airway inflammation, prevent exacerbations, and abrogate many of the symptomatic manifestations of asthma.³⁷ Oral corticosteroids (OCSs) are also used in asthmatic patients but primarily for acute exacerbations and as maintenance therapy in patients with more severe symptoms. ICSs are particularly favored because they provide targeted anti-inflammatory benefit to the airways without subjecting patients to major systemic effects. However, ICSs are not completely void of systemic or topical side effects at higher doses in some patients.

ICSs and asthma

Expert Panel Report-3 guidelines recommend a stepwise management of asthma. In children aged 0 to 4 years, low- to medium-dose ICS monotherapy is recommended as the preferred choice for persistent asthma for step 2 to step 3 management, followed by medium- to high-dose ICSs in combination with long-acting β -agonist (LABA) or montelukast for step 4 to step 6 care. For children aged 5 to 11 years, low-dose ICS monotherapy and then either medium-dose ICS or low-dose ICS plus LABA or

TABLE II. Pharmacodynamic/pharmacokinetic variables of ICSs*

ICS	Binding affinity†	Systemic clearance (l/h)	Half-life‡ (h)	Oral bioavailability (%)	Lung delivery (%)
BDP	13.5	120	2.7	40	50-60
BUD	9.4	84	2.8	11	
DPI					15-30
Nebules					5-8
CIC	12	228	3.4	<1	50
FP MDI	18	66	7.8	≤1	20
DPI					15
MF	23	53	5.0	<1	11

Reproduced with permission from Stoloff and Kelly.³⁹

BUD, Budesonide; CIC, ciclesonide; DPI, dry-powder inhaler; FP, fluticasone propionate; MDI, metered-dose inhaler; MF, mometasone furoate.

*The values assigned to beclomethasone dipropionate and ciclesonide are for their active metabolites beclomethasone monopropionate and des-ciclesonide, respectively. Data compiled from Weinstein⁷ and Van Staa et al⁸ and the respective approved product information.

†Receptor binding affinities of ICS relative to dexamethasone equal to 1.

‡Serum half-life after intravenous administration.

montelukast is the recommended therapy for step 2 and step 3 management, respectively, whereas medium- to high-dose ICSs in combination with LABAs or montelukast are the preferred choices for step 4 to step 6 care. In adults, ICSs, either as monotherapy or in combination with LABAs, remain the preferred choice of treatment for most patients with persistent asthma (Expert Panel Report-3).

However, not all ICSs are equivalent in terms of potency and efficacy. Compared with endogenous cortisol, various formulations of ICSs possess an approximately 1000-fold greater anti-inflammatory potential.³⁸ To begin with, it might be helpful to understand the comparable doses for various ICS formulations and their categorizations that are available in the commercial market (Table I).³⁹

The chemical potency of individual preparations and the type of inhaler device play an integral role in determining comparable effects between various formulations. It is also important to consider the systemic and topical bioavailability of these formulations when assessing an ICS's side effect profile (Table II).^{7,8,39} In general and based on available data, there exists a log-linear relationship between the dose and its response (direct or indirect) for ICSs.³⁹ Improvement in lung function indices (FEV₁), changes in bronchial hyperresponsiveness, and rescue medication use are indirect clinical measures of the ICS effects, whereas modulation of inflammation (ie, changes in fraction of exhaled nitric oxide values and sputum eosinophil counts) reflect direct markers of airway inflammation.

ICSs and growth in children

Systemic adverse effects can and do occur as a result of ICS use in both children and adults, reflect an effect on bone metabolism, and include growth suppression and reduction in BMD. In childhood, there are 3 principal growth phases: a nutrition-dependent phase in infancy, a prepubertal phase dependent on growth hormone secretion, and a pubertal phase. The mechanisms by which corticosteroids affect these processes include stimulation of hypothalamic somatostatin secretion to inhibition of pulsatile release of growth hormone, downregulation of growth hormone receptors and their binding activity, and a decrease in insulin-like growth factor 1 levels. In prepubertal children, a reduction in growth velocity for the first few years of therapy has been found with low- to medium-dose ICS use, with an average growth reduction of approximately 1 cm.⁴⁰⁻⁴⁵ The Childhood

Asthma Management Program (CAMP) compared the effects of long-term use of 200 µg of budesonide twice daily, 4 mg of nedocromil twice daily, and placebo in 1041 children. The investigators initially concluded that although there was a measurable decrement in growth velocity, there was not an influence on eventual adult height. However, the same study group, in their most recent follow-up assessment of the CAMP study, concluded that there was a 1.2-cm ($P = .001$) reduction in adult height achieved in the budesonide-treated group compared with the placebo-treated group. In subgroup analyses this height decrement was found to be particularly significant for female patients, who had a reduction of 1.8 cm in height ($P = .001$) and also for children who were younger at enrollment (age, 5-8 years; -1.9 cm; $P = .004$). Finally, the effect was more pronounced when a larger daily dose of ICS was used in the first 2 years of therapy.⁴⁶

The findings from CAMP are not universal, and other retrospective studies to evaluate the effect of ICS use in childhood on eventual adult height have not found similar results.⁴⁷⁻⁴⁹ In one study of 142 children who were treated with varying doses of budesonide for approximately 9 years, no significant differences in adult height were demonstrated when compared with predicted height.⁵⁰ In a small study of 24 asthmatic children aged 6 to 12 years, 40 to 160 µg/d inhaled ciclesonide had no effect on short-term lower-leg growth rate.⁵¹ Finally, a Cochrane review compared intermittent versus daily ICSs in 532 children and adults with asthma and suggested that there was a modest suppression in growth (-0.41 cm) in the group treated daily compared with those undergoing intermittent treatment.⁵² Collectively, these data suggest that a small yet clinically significant and persistent growth retardation is possible with long-term ICS use in childhood, even at low to medium doses. However, these reassuring findings should be weighed carefully against the potential for greater growth retardation that might result should frequent asthma exacerbations occur by withholding ICS therapy, thus necessitating frequent OCS bursts.

ICS use and BMD in children and adults

Although growth is of paramount importance for pediatricians, bone density/quality and fragility fractures are a concern for both adult and pediatric providers. A Cochrane systematic review on the effect of ICSs on BMD in patients with asthma and mild chronic obstructive pulmonary disease included 7 studies on 1989

TABLE III. Risk factors for osteoporosis

Advanced age (>60 y)
Low body mass index (<24 kg/m ²)
Underlying disease (RA, PMR, IBD, COPD, transplantation)
Prevalent fractures, smoking, excessive alcohol consumption, frequent falls, family history of hip fracture
Glucocorticoid receptor genotype
Increased 11 β -HSD1 expression
High glucocorticoid dose (high current or cumulative dose; long duration of therapy)
Low BMD

COPD, Chronic obstructive pulmonary disease; *IBD*, inflammatory bowel disease; *PMR*, polymyalgia rheumatica; *RA*, rheumatoid arthritis.

subjects aged 30 to 52 years and found no evidence of increased risk of BMD loss, bone turnover, or vertebral fractures (odds ratio [OR], 1.87; 95% CI, 0.5-7.03) in the ICS-treated group compared with the placebo-treated group at 2 to 3 years' follow-up. The patients in this analysis were treated with conventional ICS doses (0.2-4 mg/d beclomethasone equivalent) for 2 or 3 years.⁵³ Another meta-analysis, which included 5 case-control studies of 43,783 patients who received ICSs and 259,936 control subjects, found a 12% increase in nonvertebral fractures (OR, 1.12; 95% CI, 1.00-1.26) for each 1000 μ g/d increase in the dose of beclomethasone dipropionate (BDP) or equivalent.⁵⁴ A large retrospective cohort study to evaluate the use of ICSs and fracture risk included 170,818 subjects who used ICSs, 170,818 control subjects, and 108,786 subjects who used a bronchodilator alone. The findings indicated that the adjusted OR among ICS users compared with control subjects for nonvertebral, hip, and vertebral fractures to be 1.15, 1.22, and 1.51, respectively. No differences in adjusted ORs were noted between the ICS- and bronchodilator-treated groups. The authors suggested that the increased risk in fractures might be due to the underlying respiratory disease rather than the ICS use.⁵⁵ Two additional studies with patients who used high-dose BDP for 1 year revealed variable effects: no significant change in BMD⁵⁶ versus a significantly lower BMD in the ICS-treated group.⁵⁷ Another study concluded that a dose of 2000 μ g/d BDP for 7 years is associated with a BMD that is 1 SD lower than that seen in patients receiving 200 μ g/d for 1 year.⁵⁸ Overall, the data for the effect of ICSs on the BMD of adults demonstrate conflicting results, with a trend toward diminished BMD and increased fracture risk for patients receiving long-term moderate- to high-dose ICS. Caution should be exercised, particularly in patients who are already at increased risk for osteoporosis and fractures at baseline (Table III).

The effect of ICSs on BMD in children is more complex, and the outcomes are more variable. In a United Kingdom study of children aged 4 to 17 years, the relative risk for a nonvertebral fracture appeared to increase with larger daily doses of ICSs, with a relative risk of 1.10 for an average beclomethasone dose of less than 200 μ g/d, 1.23 for doses of 201 to 400 μ g/d, and 1.36 for doses of greater than 400 μ g/d. However, the excess risk disappeared after adjusting for markers of asthma severity, suggesting that the observed effect might be due partially to the respiratory disease rather than ICS use alone.⁵⁹ Another study of 48 asthmatic prepubertal children revealed a reduction in BMD for those treated with either BDP or budesonide.⁶⁰ In contrast, the CAMP study group concluded that no significant differences in BMD were noted between budesonide or nedocromil or placebo therapy⁴⁴; however,

a small reduction in bone mineral accretion (without an accompanying risk for osteopenia) from ICS use was noted in boys.⁶¹

Another study of asthmatic children receiving long-term, high-dose fluticasone propionate (average, 771.2 μ g/d) showed no significant changes in bone metabolism or BMD compared with control subjects.⁶² A similar conclusion was observed by Gregson et al⁶³ in children with moderate-to-severe asthma treated with fluticasone propionate (200 μ g/d) or BDP (400 μ g/d) for 82 weeks, and neither dosing schedule had an effect on BMD.⁶³ Overall, existing data suggest that the relationship between ICS use and BMD in children is conflicting and confounded by numerous other variables and awaits further evaluation. Impairment of BMD as a result of HPA axis suppression from long-term high-dose ICS use also requires further study.

OCS use in asthma and effect on growth

OCSs are an effective intervention to treat flares of many immune-mediated diseases, including asthma exacerbations. EPR-3 guidelines also recommend consideration of long-term OCSs at step 6 care for severe persistent asthma. Contrary to the experience with ICSs, the evidence for OCSs and their effects on growth and BMD is unambiguous. Low doses of prednisone (2.5 and 5 mg/d) administered for a short duration (2 $\times$ 2 weeks) to prepubertal asthmatic children significantly decreased short-term leg growth (-0.64 and -0.54 mm/wk) when measured by means of knemometry.⁶⁴ A meta-analysis of 21 studies of 810 asthmatic children concluded that there was a significant but weak tendency for OCS use in asthmatic patients to be associated with growth impairment.⁶⁵ Additionally, in infants treated for hemangiomas, Pope et al⁶⁶ demonstrated that the long-term use of prednisone (2 mg/kg/d for 3 months followed by a 6- to 9-m taper) resulted in greater growth suppression than pulse dosing of corticosteroids (30 mg/d $\times$ 3 days) administered monthly for 3 consecutive months.⁶⁶ In another study of children with severe asthma receiving high-dose ICSs plus either intermittent, alternate, or daily OCSs, significant growth suppression (SDs, -0.44 , -1.22 , and -0.93 , respectively) was noted with each OCS regimen. The effect on growth was greater when the dosage of prednisone exceeded 10 mg every other day.⁶⁷

OCS use in asthmatic patients and BMD in children and adults

OCS use also has a more profound effect on BMD, leading to osteoporosis and increasing the fracture risk for adults.^{4,6-8,10,11,68} This relationship is less definitive and more variable in children. The CAMP study evaluated a cohort of children aged 5 to 12 years with mild-to-moderate asthma. In boys, OCS use, when administered as bursts, was found to adversely affect bone mineral accretion in a dose-dependent manner and posed an increased risk (10%, 14%, and 21%, respectively; $P = .02$) of osteopenia for 0, 1 to 4, and 5 or more courses of prednisone. As noted previously, a smaller decrease in bone mineral accretion was noted in boys with long-term ICS use but without an increased risk for osteopenia.⁶¹ The previously mentioned study by Covar et al⁶⁷ in children with severe asthma revealed lower z scores (-0.7 , -0.98 , and -1.26 , respectively) for intermittent, alternate, and daily OCS use. The risk for osteopenia was significantly greater in children who received more than 10 mg

TABLE IV. Recommendations on counseling for lifestyle modification and assessment of patients starting glucocorticoids at any dose with an anticipated duration of 3 months or greater

Recommendation	Level of evidence
Weight-bearing activities	C
Smoking cessation	C
Avoidance of excessive alcohol intake (>2 drinks per day)	C
Nutritional counseling on calcium and vitamin D intake	C
Fall risk assessment	C
Baseline dual x-ray absorptiometry	C
Serum 25-hydroxyvitamin D level	C
Baseline height	C
Assessment of prevalent fragility fractures	C
Consider radiographic imaging of the spine or vertebral fracture assessment for those initiating or currently receiving prednisone ≥ 5 mg/d or its equivalent	C
Calcium intake (supplement plus oral intake) 1200-1500 mg/d*	A
Vitamin D supplementation	A

Reproduced with permission from Grossman et al.²

*Recommendations for calcium and vitamin D supplementation are for any dose or duration of glucocorticoids rather than a duration of greater than 3 months.

of prednisone every other day compared with lower doses (69% vs 21%, $P < .003$) and was also highly correlated with growth suppression. Another cross-sectional study⁶⁹ on prepubertal asthmatic children revealed a significantly lower weight-adjusted lumbar spine BMD in patients treated with high-dose ICSs plus intermittent doses of OCSs compared with ICS treatment alone (mean difference, 0.06 g/cm²; 95% CI, -0.02 to -0.10). In contrast, a cross-sectional study of children aged 2 to 17 years found no difference in BMD z scores with repeated short bursts of systemic corticosteroids compared with z scores in those who did not receive this treatment.⁷⁰

In asthmatic adults, a decrease in BMD was observed in patients receiving frequent OCS bursts.⁷¹ A similar result, as well as an increased risk for vertebral osteoporosis, was found in a study of older men with either chronic obstructive pulmonary disease or asthma who received either OCSs or ICSs.⁷² In a study of 53 asthmatic adults treated long-term with high-dose ICSs (budesonide or beclomethasone, 1.5 g/d for ≥ 12 months) with or without prior OCS use, lumbar spine and proximal femur BMDs were 1 SD lower for those taking OCSs or high-dose ICSs, which roughly equates to a doubling of the risk of fracture at these sites.⁷³ In summary, chronic and perhaps even intermittent use of OCSs has the potential to cause a decrease in BMD and increase the risk for osteoporosis and fractures in both children and adults. Therefore it is incumbent on every clinician to carefully weigh the potential benefit (preventing the loss of asthma control) against this risk before opting to prescribe long-term or short-term OCS therapy.

REVIEW OF THE 2010 ACR GIO GUIDELINES

In 2010, the ACR updated its recommendations on GIO management²; this revision has led to “a more targeted, but more complicated” guideline.⁷⁴ The American Society for Bone and Mineral Research (ASBMR) professional practice committee reviewed these guidelines and made suggestions to simplify some of the recommendations.³

The ACR panel agreed that the management of GIO requires a multifaceted strategy that attempts to optimize all possible risk factors involved. Lifestyle modifications were recommended for all patients starting glucocorticoids at any dose for 3 or more months (Table IV).² It should be noted that apart from vitamin D and calcium supplementation, all recommendations have an evidence grade of C. Recently, intense debate regarding calcium and vitamin D supplementation has developed, which has caused confusion among patients and health care providers, but this will not be discussed here. However, it is our opinion that health care providers should ensure adequate calcium and vitamin D intake for all patients, regardless of the dose and duration of glucocorticoid use, as recommended by the ACR. Recognizing the controversial nature of these topics, the National Osteoporosis Foundation recommendations of approximately 1200 mg of calcium and 800 to 1000 IU of vitamin D daily seem reasonable.

According to the ACR GIO guidelines, adding a pharmacologic agent for GIO should be considered if glucocorticoid therapy is anticipated to be longer than 3 months. It is important to highlight that pharmacologic GIO treatment, if indicated, should start at the time when glucocorticoids are initiated and not once the patient has already received this therapy for 3 months. The decision on whether to start additional pharmacologic therapy for GIO if a glucocorticoid course of 3 months or more is anticipated should be based on 3 factors: (1) postmenopausal status for female patients or age greater than 50 years for male patients, (2) dose of glucocorticoid to be used, and (3) fracture risk calculated by using FRAX. The FRAX tool is an online resource (<http://www.shef.ac.uk/FRAX>) that was developed by the World Health Organization to estimate the 10-year absolute fracture risk based on clinical risk factors and BMD, if available. It predicts fragility fracture risk better than BMD alone.

In the ACR algorithm, the first decision point is whether the patient is postmenopausal (female patients) or 50 years and older (male patients). For premenopausal female patients and male patients younger than 50 years and children, only limited evidence exists. For premenopausal women and men younger than 50 years, the initial determination is whether the patient already has a fragility fracture (Fig 2). This assessment might include thoracic and lumbar spine radiographs or vertebral fracture assessment that can be done with the dual-energy x-ray absorptiometry (DXA) scan.^{3,75-77} “Screening” for vertebral fractures in certain older adults is recommended by the National Osteoporosis Foundation in their 2013 “Clinician’s guide.”¹²

In premenopausal women and younger men without fragility fractures, the ACR committee found inadequate evidence on which to base a recommendation, and it is up to the health care provider to have a discussion with the patient regarding the benefits and risks of pharmacologic osteoporosis therapy. If there is a prevalent fragility fracture, the overall recommendation is to initiate pharmacologic therapy. For female patients, it is important to determine whether they are of child-bearing age because there is concern that bisphosphonates can adversely affect pregnancies.⁷⁸⁻⁸⁰ Bisphosphonates have a US Food and Drug Administration (FDA) category C pregnancy risk. As a consequence, there was no consensus from the ACR panel whether pharmacologic therapy is recommended in those receiving doses of less than 7.5 mg daily of prednisone and in those receiving treatment (≥ 7.5 mg) for less than 3 months. Zoledronic acid should not be used in this group. The ACR

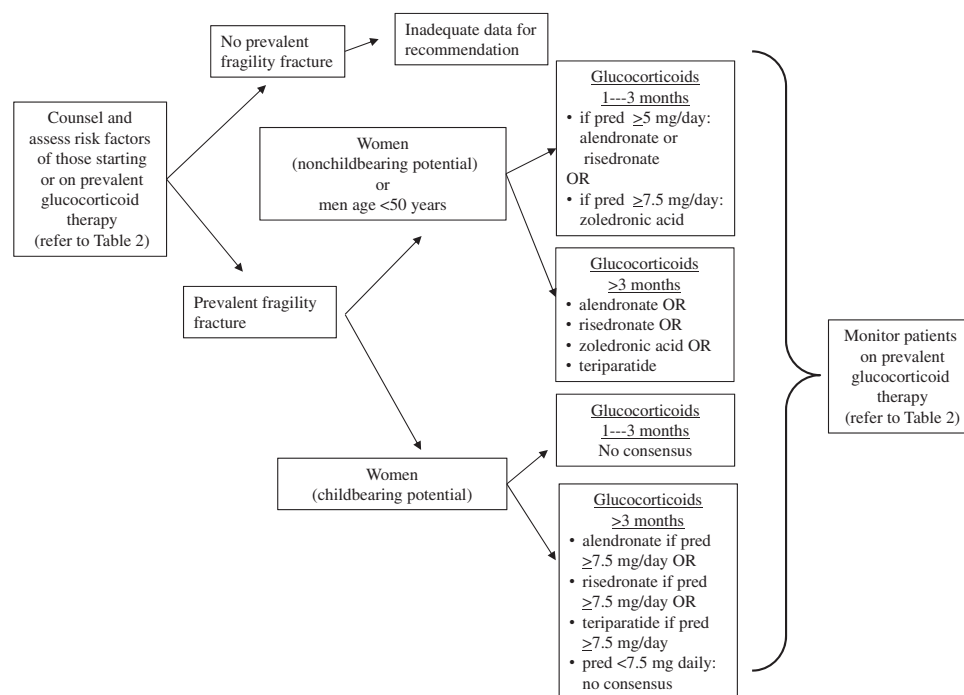


FIG 2. Approach to premenopausal women and men aged less than 50 years initiating or receiving glucocorticoid therapy. *pred*, Prednisone. Reproduced with permission from Grossman et al.²

TABLE V. Treatment of premenopausal infertile women and men less than 50 years of age

		Prevalent fracture	
		Prednisone ≤3 mo	Prednisone >3 mo
ASBMR PPC*	Consider therapy if z score −2.0 or significant decrease in BMD related to glucocorticoid therapy	Bisphosphonate†	Bisphosphonate† or teriparatide
Comparison with ACR guidelines‡	ACR committee found inadequate data for this subgroup	ACR committee recommended zoledronate only if prednisone dose ≥7.5 mg/d	Agreement

Reproduced with permission from Hansen et al.³

*Consensus of the ASBMR Professional Practice Committee.

†Treatment with alendronate, risedronate, or zoledronate, which are all FDA approved for the treatment of GIO.

‡ACR 2010 guidelines for the prevention and treatment of GIO.

panel did recommend teriparatide as an alternative treatment agent in premenopausal female patients who are not of childbearing age and male patients younger than 50 years. They did not make this recommendation for female patients who are fertile.

The ASBMR panel reviewed the ACR guidelines and suggested that treatment should also be considered in those with BMD z scores of less than −2.0 and in those with a significant decrease in BMD related to glucocorticoid treatment (Tables V and VI).³ They also suggested that teriparatide could be considered as an alternative in this population.³ It should be noted that teriparatide also has FDA category C pregnancy risk and that contraception is recommended for all pharmacologic osteoporosis treatments.³

Pharmacologic treatment of GIO in children is even more controversial because of inadequate data.^{13,14,81} There is expert consensus that children and adolescents who are at increased risk for fragility fractures should be identified.¹³ As noted earlier, children who receive glucocorticoids are at higher fragility fracture risk. However, no clear guidelines exist on how these

patients should be identified and what the evaluation for fracture risk should entail. BMD and previous vertebral fracture can be assessed with DXA technology.⁸² Interpretation of these results is difficult and does not easily translate into management decisions.^{13,14,81,83} Practically speaking, it is our opinion that all children and adolescents receiving glucocorticoids should have a review of their bone health (ie, monitoring of growth and review of possible fragility fractures) and provision of adequate calcium and vitamin D. For those with a higher fracture risk (long-term and/or high-dose glucocorticoid use, prevalent fragility/low trauma fractures, or growth problems), further evaluation might be indicated, which could include BMD measurements and assessments for vertebral fractures. No pharmacologic therapy has been approved for the treatment of fragility fractures/osteoporosis in children and adolescents. Bisphosphonates have been used successfully in these age groups to treat secondary osteoporosis, such as GIO, and other diseases, such as osteogenesis imperfecta.⁸¹ However, concerns remain about the long-term safety (because these agents are deposited in bone) and efficacy because only limited data are

TABLE VI. Treatment of premenopausal fertile women

	No prevalent fracture	Prevalent fracture	
		Prednisone ≤ 3 mo	Prednisone > 3 mo
ASBMR PPC*	Consider therapy if z score ≤ -2.0 or significant decrease in BMD related to ongoing glucocorticoid therapy	Little data to support therapy	Preference for short-acting drugs, such as teriparatide or denosumab instead of bisphosphonates†
Comparison with ACR guidelines‡	ACR committee found inadequate data for this subgroup	Agreement	No consensus if prednisone dose < 7.5 mg/d; alendronate, risedronate, or zoledronate (not teriparatide) if prednisone dose ≥ 7.5 mg/d

Reproduced with permission from Hansen et al.³ Contraception is recommended for all fertile women, regardless of which therapy is chosen.

*Consensus of the ASBMR Professional Practice Committee.

†Treatment with alendronate, risedronate, or zoledronate, which are all FDA approved for the treatment of GIO.

‡ACR 2010 guidelines for the prevention and treatment of GIO.

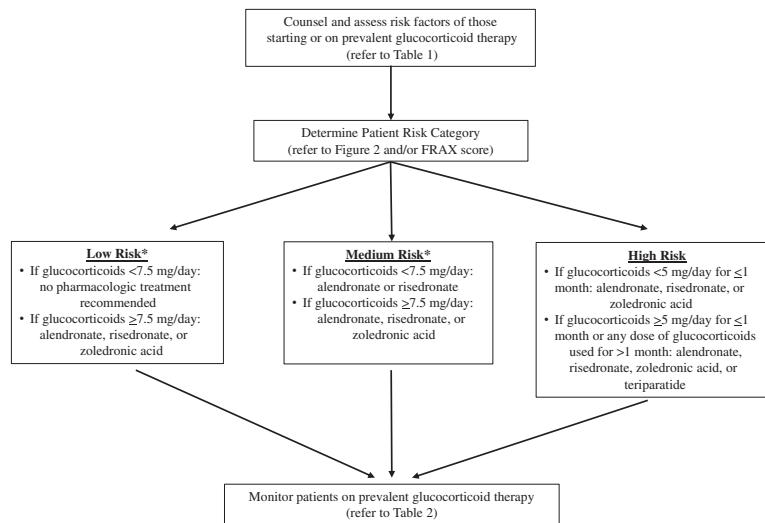


FIG 3. Approach to postmenopausal women and men aged greater than 50 years initiating or receiving glucocorticoid therapy. *For low- and medium-risk patients, recommendations are for an anticipated or prevalent duration of 3 or more months of glucocorticoids. Reproduced with permission from Grossman et al.²

available.^{84,85} For now, their use should be restricted to those patients with high fracture risk (patients with prevalent fragility fractures and low BMD) and not used as standard therapy.^{13,14,85,86}

The ACR recommendations for management of GIO in postmenopausal female patients and male patients older than 50 years should be based on FRAX risk and glucocorticoid doses with thresholds of 7.5 mg of prednisone (or equivalent) for the low- and medium-risk categories and 5 mg of prednisone (equivalent) for the high-risk category. The FRAX absolute fracture risk thresholds suggested by the ACR panel are less than 10% for low risk, 10% to 20% for medium risk, and greater than 20% for high risk (Fig 3). No pharmacologic intervention is suggested in a low-risk patient with glucocorticoid dosing of less than 7.5 mg of prednisone. If dosing exceeds 7.5 mg of prednisone, bisphosphonate therapy is recommended for all risk groups and dosing. With regard to individual bisphosphonates, the strength of evidence to recommend alendronate and risedronate is superior to that of zoledronic acid and not necessarily because zoledronic acid is less potent but because there is insufficient evidence available. Teriparatide (recombinant parathyroid hormone) could be substituted for a bisphosphonate

in a high-risk patient taking a glucocorticoid dose of greater than 5 mg/d prednisone for less than 1 month or any glucocorticoid dose for greater than 1 month. A summary of ACR/ASBMR-recommended medications for GIO is shown in Table VII.

The Professional Practice Committee of the ASBMR largely agreed with the ACR recommendations for postmenopausal female patients and male patients older than 50 years, with some subtle variations for the medium- and high-risk populations; these modifications make the management approach more straightforward. They recommend treatment with a bisphosphonate (alendronate, risedronate, or zoledronate) for those with a medium risk and treatment with any bisphosphonate or teriparatide for those at high risk, regardless of the glucocorticoid treatment duration and regardless of whether the glucocorticoid dose is greater than or less than 7.5 mg/d prednisone (equivalent; Table VIII).³ The ACR panel did not include denosumab, a humanized mAb to the receptor activator of nuclear factor κ B ligand, in their recommendations because it has not yet been approved for GIO. However, it is approved by the FDA for the prevention of fractures in postmenopausal women with osteoporosis. The ASBMR task force believed that denosumab could

TABLE VII. ACR/ASBMR-recommended pharmacotherapy for GIO

Medication	Dosage/route	Side effects/notes
Alendronate	70 mg by mouth weekly	Dyspepsia, abdominal pain, musculoskeletal pain
Risedronate	35 mg by mouth weekly, 150 mg by mouth monthly	Rash, abdominal pain, dyspepsia, diarrhea, arthralgia
Zoledronic acid	5 mg/y administered intravenously	Acute inflammatory reaction (flu-like symptoms, fever, myalgia) within 3 d of infusion; hypotension, fatigue, eye inflammation, nausea, vomiting, abdominal pain
Teriparatide	20 µg/d administered subcutaneously	Transient hypercalcemia, nausea, rhinitis, arthralgia, pain
Denosumab*	60 mg every 6 mo administered subcutaneously	Dermatitis, rash, mild bone/muscle pain, UTIs; can use in patients with CrCl ≤30 mL/min

CrCl, Creatinine clearance; UTI, urinary tract infection.

*Not approved by the FDA for GIO.

TABLE VIII. Treatment of postmenopausal women and men older than 50 years

	Low risk	Medium risk	High risk
ASBMR RPC*	Prednisone <7.5 mg/d: if no therapy given, monitor closely for prevalent fracture and decrease in BMD Prednisone ≥7.5 mg/d: bisphosphonate†	Bisphosphonate†	Bisphosphonate† or teriparatide
Comparison with ACR‡	Agreement	ACR recommend zoledronate only in patients taking ≥7.5 mg/d prednisone	ACR recommended teriparatide only in patients taking glucocorticoids >1 mo or ≥5 mg/d for <1 mo

Reproduced with permission from Hansen et al.³

*Consensus of the ASBMR Professional Practice Committee.

†Treatment with alendronate, risedronate, or zoledronate, which are all FDA approved for the treatment of GIO.

‡ACR 2010 guidelines for the prevention and treatment of GIO.

TABLE IX. Simplified algorithm for GIO management

Fragility fracture status	Glucocorticoid dose (prednisone equivalent, treatment ≥3 mo duration)	Premenopausal patients/male patients, age <50 y		Postmenopausal patients/male patients, age ≥50 y		
		Premenopausal female, fertile†	Premenopausal female, non-child bearing/male patients age <50 y	Low FRAX risk (<10%)	Medium FRAX risk (10% to 20%)	High FRAX risk (>20%)‡
Yes	<5-7.5 mg/d	No*	Yes	Yes	Yes	Yes
	≥5-7.5 mg/d	Yes	Yes	Yes	Yes	Yes
No	<5-7.5 mg/d	No*	No*	No	No*	Yes
	≥5-7.5 mg/d	No*	Yes	Yes	Yes	Yes

Yes indicates “treat with pharmacologic osteoporosis therapy in addition to adequate calcium and vitamin D intake and regular exercise.” No indicates “treat with adequate calcium and vitamin D intake and regular exercise alone.”

*The decision not to treat with pharmacologic osteoporosis therapy should be based on the absence of additional factors, such as a significant decrease in BMD on serial DXA assessments, frequent falls, low z scores (for premenopausal female patients/male patients aged <50 years), abnormal bone turnover markers, and number of fractures, as well as the patient’s preference. Referral to an osteoporosis specialist should be considered.

†Contraception is recommended for all fertile women if pharmacologic osteoporosis therapy is being considered.

‡Add pharmacologic osteoporosis therapy regardless of the dose and length of glucocorticoid treatment.

be used for GIO based on a trial in patients with rheumatoid arthritis treated with or without glucocorticoids.⁸⁷

An attempt to simplify the complicated ACR recommendations is depicted in Table IX. We recommend that most patients with a fragility fracture, a glucocorticoid dose of 5 to 7.5 mg/d (prednisone equivalent) or greater, or both receive pharmacologic osteoporosis therapy in addition to adequate calcium and vitamin D intake. However, this is more complicated in premenopausal fertile female patients. In this group and in patients receiving prednisone (equivalent) doses of less than 5 to 7.5 mg/d, the decision to add a pharmacologic agent often depends on additional factors that might increase or decrease the risk for fragility fractures, as well as the patient’s preference. These

patients are commonly referred to an osteoporosis specialist for help with the management of their bone health.

Monitoring of GIO

To monitor for GIO, the ACR panel recommends numerous options for patients receiving protracted glucocorticoid therapy (Table X).²

It is our opinion that a DXA could be initially repeated after 1 year of GIO treatment and every 24 months thereafter in those with moderate and high fracture risk. However, it might be possible to obtain DXAs less frequently in those with low fracture risk, normal BMD, and stability of BMD.

TABLE X. Recommended monitoring for patients receiving prevalent glucocorticoid therapy for a duration of 3 months or greater

Recommendation	Level of evidence
Consider serial BMD testing	C
Consider annual serum 25-hydroxyvitamin D measurement	C
Annual height measurement	C
Assessment of incident fragility fracture	C
Assessment of osteoporosis medication compliance	C

Reproduced with permission from Grossman et al.²

AREAS OF UNCERTAINTY AND CONTROVERSY IN THE TREATMENT OF OSTEOPOROSIS

Management of patients receiving ICSs

Both the ACR panel and ASBMR Professional Practice Committee believed that there were insufficient data to make specific recommendations for children or adults receiving ICSs.⁷⁴ On the basis of current evidence, an increased fracture risk might exist from taking moderate-to-high doses of ICSs. However, it is currently difficult to establish similar dose or duration thresholds for ICSs as recommended for OCSs. For postmenopausal women and older male patients, it is possible to determine the FRAX fracture risk and then place patients in risk categories. Patients in the high-risk category should receive pharmacologic treatment, whereas patients in the moderate and low categories might not need treatment. It is our opinion that most attention should be paid to prevalent fragility fractures. Having had a fragility fracture, regardless of age, sex, type, dose, or length of glucocorticoid therapy, should encourage the health care provider to determine the risk for future fractures, recommend lifestyle modifications, and consider pharmacologic osteoporosis therapy. Until more data are available to more fully assess the effect of ICSs on fractures, this approach, in our opinion, is a reasonable pathway to start addressing GIO in those receiving ICSs.

Rare but serious side effects of antiresorptive osteoporosis medications

Bisphosphonates significantly reduce fracture risk in both patients with GIO and patients with postmenopausal/age-related osteoporosis. Depending on the fracture site, length of study, and type of bisphosphonate, the fracture risk reduction ranges from approximately 30% to approximately 70%. It is very important that the prescribing clinician reviews not only the importance of taking oral bisphosphonates correctly but also the side effects of this class of medications with their patients. Common side effects of oral bisphosphonates are gastrointestinal. Common side effects for intravenous bisphosphonates, such as zoledronate, are flu-like symptoms for a few days after the infusion; these symptoms (eg, fever and myalgia) do not reflect a medication allergy but rather release of inflammatory cytokines. Rare but widely appreciated serious side effects include osteonecrosis of the jaw and atypical femur fractures (AFFs). Current evidence suggests that there is an association between long-term bisphosphonate use and these 2 entities. If they occur, they can lead to significant morbidity and decreased quality of life for the patient. The ASBMR has published task force reports on both topics.^{88,89} Osteonecrosis of the jaw is estimated to be rare for patients receiving

osteoporosis doses of bisphosphonate therapy⁸⁹⁻⁹¹ and has recently been observed in patients treated with denosumab.^{91,92} Subtrochanteric femur fractures occur in patients who have never been treated with bisphosphonates but appear to be more common after long-term use of bisphosphonates (in addition to other risk factors, including glucocorticoid use) and have certain features that set them apart.⁸⁸ Controversy remains whether there is a causal relationship between bisphosphonates and AFFs. The ASBMR recently revised the case definition of an AFF.⁸⁸ The risk of having an AFF is related to a number of factors, including length of treatment, and ranges from 3.2 to 100 per 100,000 patient years.⁸⁸

CONCLUSION

GIO is an important concern for clinicians treating patients with ICS or OCS therapy, either continuously or intermittently. There is good evidence that oral glucocorticoids, especially when used for more than 3 months and at doses of greater than 5 to 7.5 mg/d prednisone (or equivalent), increase the risk for fragility fractures. The current evidence is less clear on the relationship of ICSs and fragility fractures, but there is concern that moderate-to-high doses of these forms of glucocorticoids decrease BMD, increase fragility fracture risk, and have a potentially negative effect on growth and adult height attained. To summarize and simplify the approach to the management of GIO, we recommend that all patients receive adequate calcium and vitamin D intake, as outlined in the ACR guidelines, and most patients with a fragility fracture, a glucocorticoid dose of 5 to 7.5 mg/d (prednisone equivalent) or greater, or both should receive pharmacologic osteoporosis therapy. In premenopausal female or male patients less than age 50 years without a fracture, a prednisone (equivalent) dose of 5 to 7.5 mg/d, or both, the decision to treat is more complex and needs to be based on additional factors influencing the risk for fragility fractures and the patient's preference. Additionally, it is our opinion that these recommendations could also be used for adults and children treated with ICSs. In cases without a clear management decision, consultation with an osteoporosis specialist might be helpful.

What do we know?

- Osteoporosis is a complication of systemic corticosteroids, a commonly used medication in the treatment of asthma.
- Risk factors for osteoporosis are known, and approaches to monitor for loss of bone mineral content are available.
- There are a number of treatment approaches for osteoporosis.

What is still unknown?

- What are the risks for osteoporosis with ICSs in asthmatic patients?
- What measures should clinicians involved in asthma care follow to prevent osteoporosis, detect osteoporosis, or both?
- What treatment options are available to the asthma clinician in the prevention, treatment, or both of osteoporosis?

REFERENCES

1. Schimmer B, Funder J. ACTH, adrenal steroids, and pharmacology of the adrenal cortex. In: Brunton L, Chabner B, Knollmann B, editors. Goodman & Gilman's

- the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill; 2011.
2. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken)* 2010;62:1515-26.
3. Hansen KE, Wilson HA, Zapalowski C, Fink HA, Minisola S, Adler RA. Uncertainties in the prevention and treatment of glucocorticoid-induced osteoporosis. *J Bone Miner Res* 2011;26:1989-96.
4. Compston J. Management of glucocorticoid-induced osteoporosis. *Nat Rev Rheumatol* 2010;6:82-8.
5. Hofbauer LC, Hamann C, Ebeling PR. Approach to the patient with secondary osteoporosis. *Eur J Endocrinol* 2010;162:1009-20.
6. Maricic M. Update on glucocorticoid-induced osteoporosis. *Rheum Dis Clin North Am* 2011;37:415-31, vi.
7. Weinstein RS. Clinical practice. Glucocorticoid-induced bone disease. *N Engl J Med* 2011;365:62-70.
8. Van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM, Cooper C. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. *Arthritis Rheum* 2003;48:3224-9.
9. Steinbuch M, Youket TE, Cohen S. Oral glucocorticoid use is associated with an increased risk of fracture. *Osteoporos Int* 2004;15:323-8.
10. Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton IL, et al. A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res* 2004;19:893-9.
11. van Staa TP. The pathogenesis, epidemiology and management of glucocorticoid-induced osteoporosis. *Calcif Tissue Int* 2006;79:129-37.
12. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Washington (DC): National Osteoporosis Foundation; 2013.
13. Bachrach LK. Consensus and controversy regarding osteoporosis in the pediatric population. *Endocr Pract* 2007;13:513-20.
14. Bianchi ML. Osteoporosis in children and adolescents. *Bone* 2007;41:486-95.
15. Leonard MB. Glucocorticoid-induced osteoporosis in children: impact of the underlying disease. *Pediatrics* 2007;119(Suppl 2):S166-74.
16. Lewiecki EM, Gordon CM, Baim S, Binkley N, Bilezikian JP, Kendler DL, et al. Special report on the 2007 adult and pediatric Position Development Conferences of the International Society for Clinical Densitometry. *Osteoporos Int* 2008;19:1369-78.
17. van Staa TP, Cooper C, Leufkens HG, Bishop N. Children and the risk of fractures caused by oral corticosteroids. *J Bone Miner Res* 2003;18:913-8.
18. von Scheven E. Pediatric bone density and fracture. *Curr Osteoporos Rep* 2007;5:128-34.
19. Ward LM. Osteoporosis due to glucocorticoid use in children with chronic illness. *Hormone Res* 2005;64:209-21.
20. Zhang C, Liu Z, Klein GL. Overview of pediatric bone problems and related osteoporosis. *J Musculoskelet Neuronal Interact* 2012;12:174-82.
21. Burnham JM. Inflammatory diseases and bone health in children. *Curr Opin Rheumatol* 2012;24:548-53.
22. Rodd C, Lang B, Ramsay T, Alos N, Huber AM, Cabral DA, et al. Incident vertebral fractures among children with rheumatic disorders 12 months after glucocorticoid initiation: a national observational study. *Arthritis Care Res (Hoboken)* 2012;64:122-31.
23. Schuit SCE, van der Klift M, Weel AEAM, de Laet CEDH, Burger H, Seeman E, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam study. *Bone* 2004;34:195-202.
24. Bouxsein ML. Determinants of skeletal fragility. *Best Pract Res Clin Rheumatol* 2005;19:897-911.
25. Bonewald LF. The amazing osteocyte. *J Bone Miner Res* 2011;26:229-38.
26. Frost HM. A 2003 update of bone physiology and Wolff's Law for clinicians. *Angle Orthod* 2004;74:3-15.
27. den Uyl D, Bultink IE, Lems WF. Glucocorticoid-induced osteoporosis. *Clin Exp Rheumatol* 2011;29(Suppl):S93-8.
28. Horlings CG, van Engelen BG, Allum JH, Bloem BR. A weak balance: the contribution of muscle weakness to postural instability and falls. *Nat Clin Pract Neurol* 2008;4:504-15.
29. Pfeifer M, Sinaki M, Geusens P, Boonen S, Preisinger E, Minne HW, et al. Musculoskeletal rehabilitation in osteoporosis: a review. *J Bone Miner Res* 2004;19:1208-14.
30. Bischoff-Ferrari HA. The role of falls in fracture prediction. *Curr Osteoporos Rep* 2011;9:116-21.
31. Masud T, Binkley N, Boonen S, Hannan MT. FRAX(®) Position Development Conference Members. Official positions for FRAX® clinical regarding falls and frailty: can falls and frailty be used in FRAX®? From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX(R). *J Clin Densitom* 2011;14:194-204.
32. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013;368:2455-66.
33. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985-93.
34. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973-84.
35. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011;365:1088-98.
36. Busse WW, Holgate S, Kerwin EM, Chon Y, Feng JY, Lin JH, et al. A randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety, tolerability, and efficacy of brodalumab (AMG 827) in subjects with moderate to severe asthma. Abstract presented at: American Academy of Allergy, Asthma & Immunology Annual Meeting; San Antonio, Texas; February 22-26, 2013 (AB230).
37. Durran SR, Viswanathan RK, Busse WW. What effect does asthma treatment have on airway remodeling? Current perspectives. *J Allergy Clin Immunol* 2011;128:439-50.
38. Derendorf H, Nave R, Drollmann A, Cerasoli F, Wurst W. Relevance of pharmacokinetics and pharmacodynamics of inhaled corticosteroids to asthma. *Eur Respir J* 2006;28:1042-50.
39. Stoloff SW, Kelly HW. Updates on the use of inhaled corticosteroids in asthma. *Curr Opin Allergy Clin Immunol* 2011;11:337-44.
40. Ferguson AC, Van Bever HP, Teper AM, Lasysya O, Goldfrad CH, Whitehead PJ. A comparison of the relative growth velocities with budesonide and fluticasone propionate in children with asthma. *Respir Med* 2007;101:118-29.
41. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefer SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985-97.
42. Pedersen S, Warner J, Wahn U, Staab D, Le Bourgeois M, Van Essen-Zandvliet E, et al. Growth, systemic safety, and efficacy during 1 year of asthma treatment with different beclomethasone dipropionate formulations: an open-label, randomized comparison of extrafine and conventional aerosols in children. *Pediatrics* 2002;109:e92.
43. Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. *Pediatrics* 2000;106:E8.
44. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054-63.
45. Kelly HW, Nelson HS. Potential adverse effects of the inhaled corticosteroids. *J Allergy Clin Immunol* 2003;112:469-79.
46. Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012;367:904-12.
47. Inoue T, Doi S, Takamatsu I, Murayama N, Kameda M, Toyoshima K. Effect of long-term treatment with inhaled beclomethasone dipropionate on growth of asthmatic children. *J Asthma* 1999;36:159-64.
48. Silverstein MD, Yunginger JW, Reed CE, Petterson T, Zimmerman D, Li JT, et al. Attained adult height after childhood asthma: effect of glucocorticoid therapy. *J Allergy Clin Immunol* 1997;99:466-74.
49. Van Bever HP, Desager KN, Lijssens N, Weyler JJ, Du Caju MV. Does treatment of asthmatic children with inhaled corticosteroids affect their adult height? *Pediatr Pulmonol* 1999;27:369-75.
50. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000;343:1064-9.
51. Agertoft L, Pedersen S. Short-term lower-leg growth rate and urine cortisol excretion in children treated with ciclesonide. *J Allergy Clin Immunol* 2005;115:940-5.
52. Chauhan BF, Chartrand C, Ducharme FM. Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults. *Cochrane Database Syst Rev* 2013;(2):CD009611.
53. Jones A, Fay JK, Burr M, Stone M, Hood K, Roberts G. Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2002;(1):CD003537.
54. Weatherall M, James K, Clay J, Perrin K, Masoli M, Wijesinghe M, et al. Dose-response relationship for risk of non-vertebral fracture with inhaled corticosteroids. *Clin Exp Allergy* 2008;38:1451-8.
55. van Staa TP, Leufkens HG, Cooper C. Use of inhaled corticosteroids and risk of fractures. *J Bone Miner Res* 2001;16:581-8.

56. Herralta J, Puolijoki H, Impivaara O, Liippo K, Tala E, Nieminen MM. Bone mineral density in asthmatic women on high-dose inhaled beclomethasone dipropionate. *Bone* 1994;15:621-3.
57. Packe GE, Douglas JG, McDonald AF, Robins SP, Reid DM. Bone density in asthmatic patients taking high dose inhaled beclomethasone dipropionate and intermittent systemic corticosteroids. *Thorax* 1992;47:414-7.
58. Wong CA, Walsh LJ, Smith CJ, Wisniewski AF, Lewis SA, Hubbard R, et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet* 2000;355:1399-403.
59. van Staa TP, Bishop N, Leufkens HG, Cooper C. Are inhaled corticosteroids associated with an increased risk of fracture in children? *Osteoporos Int* 2004;15:785-91.
60. Allen HD, Thong IG, Clifton-Bligh P, Holmes S, Nery L, Wilson KB. Effects of high-dose inhaled corticosteroids on bone metabolism in prepubertal children with asthma. *Pediatr Pulmonol* 2000;29:188-93.
61. Kelly HW, Van Natta ML, Covar RA, Tonascia J, Green RP, Strunk RC. Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the childhood Asthma Management Program (CAMP) study. *Pediatrics* 2008;122:e53-61.
62. Griffiths AL, Sim D, Strauss B, Rodda C, Armstrong D, Freezer N. Effect of high-dose fluticasone propionate on bone density and metabolism in children with asthma. *Pediatr Pulmonol* 2004;37:116-21.
63. Gregson RK, Rao R, Murrills AJ, Taylor PA, Warner JO. Effect of inhaled corticosteroids on bone mineral density in childhood asthma: comparison of fluticasone propionate with beclomethasone dipropionate. *Osteoporos Int* 1998;8:418-22.
64. Wolthers OD, Pedersen S. Short term linear growth in asthmatic children during treatment with prednisolone. *BMJ* 1990;301:145-8.
65. Allen DB, Mullen M, Mullen B. A meta-analysis of the effect of oral and inhaled corticosteroids on growth. *J Allergy Clin Immunol* 1994;93:967-76.
66. Pope E, Krafchik BR, Macarthur C, Stempak D, Stephens D, Weinstein M, et al. Oral versus high-dose pulse corticosteroids for problematic infantile hemangiomas: a randomized, controlled trial. *Pediatrics* 2007;119:e1239-47.
67. Covar RA, Leung DY, McCormick D, Steelman J, Zeitler P, Spahn JD. Risk factors associated with glucocorticoid-induced adverse effects in children with severe asthma. *J Allergy Clin Immunol* 2000;106:651-9.
68. Mazziotti G, Giustina A, Canalis E, Bilezikian JP. Glucocorticoid-induced osteoporosis: clinical and therapeutic aspects. *Arq Bras Endocrinol Metabol* 2007;51:1404-12.
69. Harris M, Hauser S, Nguyen TV, Kelly PJ, Rodda C, Morton J, et al. Bone mineral density in prepubertal asthmatics receiving corticosteroid treatment. *J Paediatr Child Health* 2001;37:67-71.
70. Ducharme FM, Chabot G, Polychronakos C, Glorieux F, Mazer B. Safety profile of frequent short courses of oral glucocorticoids in acute pediatric asthma: impact on bone metabolism, bone density, and adrenal function. *Pediatrics* 2003;111:376-83.
71. Matsumoto H, Ishihara K, Hasegawa T, Umeda B, Niimi A, Hino M. Effects of inhaled corticosteroid and short courses of oral corticosteroids on bone mineral density in asthmatic patients: a 4-year longitudinal study. *Chest* 2001;120:1468-73.
72. Dam TT, Harrison S, Fink HA, Ramsdell J, Barrett-Connor E. Osteoporotic Fractures in Men Research Group. Bone mineral density and fractures in older men with chronic obstructive pulmonary disease or asthma. *Osteoporos Int* 2010;21:1341-9.
73. Ebeling PR, Erbas B, Hopper JL, Wark JD, Rubinfeld AR. Bone mineral density and bone turnover in asthmatics treated with long-term inhaled or oral glucocorticoids. *J Bone Miner Res* 1998;13:1283-9.
74. Deal CL. Recent recommendations on steroid-induced osteoporosis: more targeted, but more complicated. *Cleve Clin J Med* 2013;80:117-25.
75. Fuerst T, Wu C, Genant HK, von Ingersleben G, Chen Y, Johnston C, et al. Evaluation of vertebral fracture assessment by dual X-ray absorptiometry in a multicenter setting. *Osteoporos Int* 2009;20:1199-205.
76. Buehring B, Krueger D, Checovich M, Gemar D, Vallarta-Ast N, Genant HK, et al. Vertebral fracture assessment: impact of instrument and reader. *Osteoporos Int* 2010;21:487-94.
77. Schousboe JT, Vokes T, Broy SB, Ferrar L, McKiernan F, Roux C, et al. Vertebral Fracture Assessment: the 2007 ISCD Official Positions. *J Clin Densitom* 2008;11:92-108.
78. Bhalla AK. Management of osteoporosis in a pre-menopausal woman. *Best Pract Res Clin Rheumatol* 2010;24:313-27.
79. McNicholl DM, Heaney LG. The safety of bisphosphonate use in pre-menopausal women on corticosteroids. *Curr Drug Saf* 2010;5:182-7.
80. Stathopoulos IP, Liakou CG, Katsalira A, Trovas G, Lyritis GG, Papaioannou NA, et al. The use of bisphosphonates in women prior to or during pregnancy and lactation. *Hormones* 2011;10:280-91.
81. Kamboj MK. Metabolic bone disease in adolescents: recognition, evaluation, treatment, and prevention. *Adolesc Med State Art Rev* 2007;18:24-46, viii.
82. Baim S, Leonard MB, Bianchi ML, Hans DB, Kalkwarf HJ, Langman CB, et al. Official Positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Pediatric Position Development Conference. *J Clin Densitom* 2008;11:6-21.
83. Bogunovic L, Doyle SM, Vogiatzi MG. Measurement of bone density in the pediatric population. *Curr Opin Pediatr* 2009;21:77-82.
84. Bachrach LK, Ward LM. Clinical review 1: Bisphosphonate use in childhood osteoporosis. *J Clin Endocrinol Metab* 2009;94:400-9.
85. Ward L, Tricco AC, Phuong P, Cranney A, Barrowman N, Gaboury I, et al. Bisphosphonate therapy for children and adolescents with secondary osteoporosis. *Cochrane Database Syst Rev* 2007;(4):CD005324.
86. Papapoulos SE. Bisphosphonate therapy in children with secondary osteoporosis. *Horm Res Paediatr* 2011;76(Suppl 1):24-7.
87. Dore RK, Cohen SB, Lane NE, Palmer W, Shergy W, Zhou L, et al. Effects of denosumab on bone mineral density and bone turnover in patients with rheumatoid arthritis receiving concurrent glucocorticoids or bisphosphonates. *Ann Rheum Dis* 2010;69:872-5.
88. Shane E, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, Cheung AM, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American society for bone and mineral research. *J Bone Miner Res* 2013 [Epub ahead of print].
89. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2007;22:1479-91.
90. Silverman SL, Landesberg R. Osteonecrosis of the jaw and the role of bisphosphonates: a critical review. *Am J Med* 2009;122(Suppl):S33-45.
91. Reid IR, Cornish J. Epidemiology and pathogenesis of osteonecrosis of the jaw. *Nat Rev Rheumatol* 2012;8:90-6.
92. Qi WX, Tang LN, He AN, Yao Y, Shen Z. Risk of osteonecrosis of the jaw in cancer patients receiving denosumab: a meta-analysis of seven randomized controlled trials. *Int J Clin Oncol* 2013 [Epub ahead of print].