Guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis in pediatrics

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ABSTRACT

Objective. To provide a framework for healthcare professionals managing pediatric patients who are on active glucocorticoid (GC) therapy and to develop recommendations for the prevention and treatment of GC-induced osteoporosis in the pediatric population.

Methods. A panel of experts on bone and pediatric diseases developed a series of PICO questions that address issues related to the prevention and treatment of osteoporosis in patients on GC therapy. In accordance with the GRADE approach, we conducted a systematic review of the literature, summarized effect estimations, and classified the quality of the evidence. Then, voting and the formulation of recommendations followed.

Results. Seven recommendations and six general principles were developed for GC-induced osteoporosis in the pediatric population.

Conclusion. These recommendations provide guidance for clinicians who must make decisions concerning pediatric patients undergoing treatment with GC.

Key words: *clinical practice guidelines; glucocorticoids; osteoporosis; pediatrics.*

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Abbreviations:
AAOMM: Argentine Association of Osteology and Mineral Metabolism
AP: alkaline phosphatase
BMC: bone mineral content
BMD: bone mineral density
DEXA: dual-energy X-ray absorptiometry
GC: glucocorticoids
GIOP: glucocorticoid-induced osteoporosis
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
IOM: Institute of Medicine
ISCD: International Society for Clinical Densitometry
IV: intravenous
JIA: juvenile idiopathic arthritis
PICO: Patient-Intervention-Comparison-Outcome
PTH: parathyroid hormone
RevMan: Review Manager
SAO: Argentine Society of Osteoporosis
SAR: Argentine Society of Rheumatology
SD: standard deviation
SLE: systemic lupus erythematosus
TBLH: total body less head
TRP: tubular reabsorption of phosphate
VFA: vertebral fracture assessment
VF: vertebral fractures

INTRODUCTION

While 60% of the peak bone mass acquisition is genetic, it is also influenced by multiple factors, such as nutritional status, calcium and vitamin D intake, physical activity, mobility, exposure to medications, chronic inflammation, and pubertal development.[1]

GIOP is one of the most common secondary causes. An adverse effect of long-term GC therapy is a reduction in BMD and/or an increase in the prevalence of brittle or osteoporotic fractures.[2–5] Bone mass loss, with predominant involvement of cancellous bone, ranges between 10% and 40% depending on the site examined, duration of treatment, underlying disease and GC used, dose and exposure time.[6–8] Fracture risk increases rapidly after initiation of GC treatment, followed by a slow but continuous phase, which reverts rapidly upon discontinuation of treatment.[9]

For this reason, to reduce the incidence of brittle fractures, an early intervention and specific measures to prevent their occurrence are required. One of the strategies in prevention is to maximize, as much as possible, the peak bone mass with targeted interventions during childhood and adolescence, taking advantage of this window of opportunity to minimize the risk of fractures.

Few studies have been conducted on GIOP prevention and treatment in pediatrics. Therefore, the theoretical framework was developed under the descriptive narrative methodology. These recommendations were made according to the GRADE methodology.

OBJECTIVES

To provide evidence-based recommendations for the prevention and treatment of GIOP in children under 18 years of age on GC therapy for more than 3 months.

Target audience

Healthcare professionals involved in the care of patients on GC therapy.

PREVALENCE OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS IN CHILDREN AND ADOLESCENTS

Decreased bone mass in children may increase the risk of fractures in childhood and, potentially, in adulthood as a result of suboptimal peak bone mass.[10–15] Other studies have evidenced the development of vertebral and long bone fractures, with a prevalence ranging between 10% and 34%.[16,17]

In the past decade, observational studies, including the Canadian steroid-induced osteoporosis in the pediatric population (STOPP) study, have revealed key clinical-biological principles regarding GIOP.[18]

Compeyrot-Lacassagne et al. studied patients with SLE and found that the prevalence of osteopenia was 37.5% and that of osteoporosis, 20.3%. However, they defined osteopenia as a Z-score between ≤ -1 and ≥ -2.5, and osteoporosis, as a Z-score < -2.5, as per a DEXA scan.[15] Other authors observed that 19% of patients had VF, with an average of 2.9 fractures per patient; of these, 56% were asymptomatic.[17]

Another study conducted in patients with rheumatic disease found a 12.4% incidence of fractures at 3 years, which was higher in the first year and was associated with a two-fold increase in the risk of fractures per 0.5 mg/kg of increase in the daily average GC dose.[18]

Marstein et al. studied bone mass in patients stratified into 2 groups by age (< 20 and ≥ 20 years old).[19] In the first group, they demonstrated a negative correlation between prednisolone (use at follow-up, monthly, and cumulative dose)

and lumbar spine Z-score, and with inflammatory markers.

The extent of involvement in bone mass depends on several factors. The decrease in Z-score as per the bone density scan in the first 6 months after starting GC therapy is another predictor of bone involvement.[18]

DIAGNOSIS

Osteoporosis in children and adolescents

A DEXA scan to assess BMD is the most adequate method for children and adolescents as per the ISCD 2019.[20]

Regions considered for assessment include the posterior-anterior spine (L1–L4) and TBLH.

Unlike in the adult population, the diagnosis of osteoporosis in children and adolescents should not be made solely on the basis of a bone densitometry value. In this population, it is also necessary to consider the presence of brittle fractures. Thus, the finding of 1 or more vertebral compression fractures is suggestive of osteoporosis in the absence of local disease or high energy trauma that could account for it.

In the absence of a VF, the presence of 2 or more long bone brittle fractures before 10 years old or 3 or more long bone fractures before 19 years old and a BMD with a Z-score ≤ -2.0 is indicative of osteoporosis in children and adolescents (*Table 1*).

For the assessment of bone health in pediatrics, it is necessary to combine the medical history and the study methodology, which can be summarized as follows:

- Medical history: anthropometry, pubertal stage.
- History and comorbidities.
- Other secondary causes.
- Lab test for phosphocalcic metabolism (*Table 2*).
- History of brittle fractures of long bones.
- X-ray of dorsal/lumbar spine or VFA.
- BMD.

Vertebral fractures

A lateral plain X-ray of the dorsolumbar spine is recommended to assess vertebral fractures. The current ISCD 2019 recommendations suggest that VFA using DEXA may replace the X-ray of the spine to assess VF.[20] In both cases, the recommended method for vertebral morphometry is Genant's semi-quantitative criteria.[21] In cases in which some vertebrae cannot be technically assessed by VFA or in which X-ray findings are not typical of an osteoporotic VF (suspicion of destructive inflammatory or malignant processes, congenital malformations, misalignments, or others), the recommendation is to perform another imaging study such as, for example, magnetic resonance imaging.

Follow-up densitometry

A DEXA bone densitometry should be performed every 6–12 months, depending on each patient. It is important to remember that, in children with short stature or stunted growth, the BMD and BMC of the spine and TBLH results should be adjusted for an adequate interpretation, using the height Z-score.

PREVENTION AND TREATMENT RECOMMENDATIONS

Methodology

The prevention and treatment recommendations were developed based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology (www.gradeworkinggroup.org) *(Supplementary material 1)*.[22]

Table 1. Interpretation of bone mineral density in pediatrics

OSTEOPOROSIS
Presence of 1 or more brittle vertebral fractures.
Presence of 2 or more brittle fractures of long bones before 10 years old and BMD with a Z-score ≤ -2.0.
Presence of 3 or more fractures of long bones before 19 years old and BMD with a Z-score ≤ -2.0.
LOW BONE MASS OR LOW BONE MINERAL DENSITY
Presence of a BMC or BMD with a Z-score below -2.0 SD.

BMD: bone mineral density.
BMC: bone mineral content.
SD: standard deviation.

Table 2. Biochemical tests to assess phosphocalcic metabolism

Complete blood count, erythrocyte sedimentation rate, CRP
Uremia, blood creatinine level, creatinine clearance
Liver function tests
Anti-transglutaminase antibodies, anti-endomysial antibodies, anti-gliadin antibodies
Serum IgA level
TSH Free T4
Total and ionized calcium levels, blood albumin level, blood phosphate level, blood magnesium level AP PTH
Vitamin 25(OH)D level
24-hour urine: urine calcium level, urine creatinine level, urine phosphate level, TRP

CRP: C-reactive protein.
Ab: antibodies.
IgA: immunoglobulin A.
TSH: thyroid stimulating hormone.
T4: thyroxine.
AP: alkaline phosphatase.
PTH: parathyroid hormone.
TRP: tubular reabsorption of phosphate.

Participation. These recommendations were developed by experts on account of the following Argentine scientific societies: AAOMM, SAO, and SAR (*Supplementary material 2*).

Literature search. The search was done in MEDLINE/PubMed, Cochrane Library, and LILACS since the beginning of each database until April 30th, 2021 (*Supplementary material 3*).

Study selection. The Rayyan software (https://rayyan-prod.qcri.org/) was used to screen literature search results. Selected articles were related to the corresponding PICO questions (*Supplementary material 4*).[22]

Data extraction and analysis. The Review Manager (RevMan) software, V.5.4.1, was used for data extraction and grouping for the statistical analysis.

Evidence reporting. Data were exported to the GRADEpro GDT software (https://gradepro.org/) to develop the GRADE tables (*Supplementary material 5*) for each PICO question. Two independent reviewers assessed the quality of evidence for each result using the GRADE quality assessment criteria.[22]

The GRADE approach rates the quality of evidence into 4 levels (high, moderate, low, or very low). In the case of a recommendation made by expert opinion consensus in the absence of evidence, the recommendation was rated as very low quality.

Rigor of development. These recommendations have been developed according to the GRADE methodology and comply with the AGREE reporting checklist to ensure the completeness and transparency of reports. A recommendation may be for or against the proposed intervention and be rated as strong or conditional.[21]

From evidence to recommendations. The GRADE methodology specifies that the expert panel makes recommendations based on the balance of benefits and harms, the quality of the evidence, and the values and preferences of parents/patients.

Consensus development. The voting panel voted on the direction and strength of the recommendation for each PICO question. The recommendations required an agreement level above 70%.[23] In some cases, the voting panel combined the PICO questions into a single recommendation for clarity. Some PICO questions were removed because the evidence was insufficient for a formal recommendation.

RESULTS

The literature review identified 361 articles; of these, only 12 scientific articles met the inclusion criteria for analysis (*Supplementary material 6*). A total of 7 recommendations (*Table 3*) and 6 general principles were developed (*Table 4*).

PREVENTION AND TREATMENT RECOMMENDATIONS

Recommendation 1. Calcium and vitamin D are strongly recommended over placebo in children and adolescents on oral GC treatment, both for prevention and in those under treatment.

Calcium and vitamin D supplementation is strongly recommended in patients on GC treatment, both for prevention and in those under

treatment for osteoporosis. This is a strong recommendation, despite the quality of the evidence, because the clinical experience and the indirect evidence support the benefits of adding these supplementation options.[24–26]

Chronic calcium deficiency resulting from inadequate intake or poor intestinal absorption is a major cause of reduced bone mass, as well as being important for peak bone mass.[27,28] Patients with a low dietary intake may increase it by consuming calcium-rich foods; supplementation should be considered when intake is insufficient (*Table 5*).[29]

Moreover, it is known that vitamin D plays an important role in calcium homeostasis and muscle function, among others.[30] The co-administration of calcium and vitamin D is superior to their administration separately.

This panel recommends measuring vitamin D levels; it is important to know calcemia and calciuria values in order to establish the best form of administration in each case.

Recommendation 2. The administration of vitamin D (on a daily/weekly/monthly basis, as applicable) is strongly recommended in children and adolescents on oral GC treatment, both for prevention and in those under treatment.

The suggested dose, depending on the child's or adolescent's age and vitamin D levels, is twice the dose required for the patient's age and physiological situation according to the IOM recommendations.[31]

For an adequate supplementation, the patient's age, place of residence, type of nutrition, other medical history related to phosphocalcic metabolism, and plasma vitamin D levels should be taken into account. Physicians should differentiate whether the patient has deficient or normal plasma levels, and provide supplementation accordingly.[32] Daily or weekly doses may be used for maintenance. These are safe doses, i.e. the likelihood of hypercalciuria is low. In pubertal children, monthly doses may be indicated if there are no contraindications.

In patients with deficiency, a new vitamin D measurement is useful. If conditions are stable, annual vitamin D measurement is recommended. Vitamin D_3 is preferred given its longer half-life.

This recommendation arises from the combination of PICO questions in the face of daily, weekly, and monthly doses at different dosages.[33]

Recommendation 3. Physical activity

Table 3. Recommendations for patients on treatment with supraphysiological doses of GC (> 8 mg m²/day of hydrocortisone or equivalent) for more than 3 months

Recommendations	Level of evidence
1. Calcium and vitamin D are strongly recommended over placebo in children and adolescents on oral GC treatment, both for prevention and in those under treatment for osteoporosis.	Very low
2. The administration of vitamin D (on a daily/weekly/monthly basis, as applicable) is strongly recommended in children and adolescents on oral GC treatment, both for prevention and in those under treatment for osteoporosis.	Very low
3. Physical activity (adequate to the underlying condition) is recommended in children and adolescents on oral GC treatment. *Expert opinion*.	Very low*
4. Alendronate is conditionally recommended over placebo in children and adolescents on chronic oral GC treatment, diagnosed with osteoporosis.	Moderate to very low
5. Risedronate is conditionally recommended over placebo in children and adolescents on chronic oral GC treatment, diagnosed with osteoporosis.	Moderate to low
6. Pamidronate is conditionally recommended over placebo in children and adolescents on chronic oral GC treatment, diagnosed with osteoporosis.	Very low
7. Zoledronic acid is suggested over placebo in children and adolescents on chronic oral GC treatment, diagnosed with osteoporosis. *Expert opinion*.	Very low*

** This recommendation is based on the consensus of expert opinion due to the absence of evidence; for this reason, it is classified as very low quality.*

Table 4. General principles

Number	*General principles*
1	An adequate clinical follow-up of the growth and development of patients on GC treatment, an adequate management of associated conditions, especially autoimmune diseases, diabetes mellitus, sarcopenia, endocrine diseases, and any other condition that may affect bone metabolism, is recommended. Also, an adequate management of other medications that could affect bone metabolism (beyond GC).
2	The gold standard method to assess BMD study is a DEXA bone densitometry, which should be performed every 6 to 12 months as long as patients remain on GC treatment or persist on GIOP treatment.
3	Biochemical assessment of bone metabolism together with an assessment of vertebral fractures is as important as BMD assessment.
4	GIOP treatment should be based on shared decisions and preferences between the parents/patient and the treating physician once the different therapeutic options available, costs, route of administration, and possible adverse effects are known.
5	The goal of GIOP treatment is to prevent the occurrence of new brittle fractures, as well as to increase BMD, as an optimal situation.
6	Treatment with GC should be limited to the minimum effective dose possible for the shortest time possible.

BMD: bone mineral density.
DEXA: dual-energy X-ray absorptiometry.
GC: glucocorticoids.
GIOP: glucocorticoid-induced osteoporosis.

Table 5. Recommendations by the Institute of Medicine (IOM) about calcium and vitamin D use in pediatrics (as modified by the IOM)[31]

Age group	Calcium (mg/day)		Vitamin D (IU/day)	
	Recommendation	Maximum use allowed	Recommendation	Maximum use allowed
0–6 months	200	1000	400	1000
6–12 months	260	1500	400	1500
1–3 years	700	2500	600	2500
4–8 years	1000	2500	600	3000
≥ 9 years	1300	3000	600	4000

(according to the underlying condition) is recommended over no physical activity in children and adolescents on oral GC treatment.

Lifestyle changes influence the acquisition of peak bone mass by 20–40%.[27,28] Changes in bone structure and composition take place during puberty and up to 30 years of age, thus influencing bone strength. It is important to understand the factors that affect bone strength early in life because a low bone strength is associated with an increased risk of fractures later in life, regardless of the incidence of falls.[34,35] The expert panel recommends physical activity based on the patient's age, current clinical condition (fracture pain), and underlying conditions, despite the lack of evidence in the literature in the pediatric population on GC treatment.

Recommendation 4. Alendronate is conditionally recommended over placebo in children and adolescents on chronic oral GC treatment, diagnosed with osteoporosis.

There are no studies providing sufficient evidence on the use of alendronate to prevent bone loss in children on GC treatment; however, there is sufficient evidence in relation to patients who require treatment.[36–39] In spite of this, in patients who already have a fracture, IV bisphosphonates are preferred because

of their greater efficacy in fracture repair and improvement of associated pain. If it is not possible to use IV bisphosphonates due to their cost or availability, oral bisphosphonates may be an option. For this reason, this is a *conditional* recommendation.

Recommendation 5. Risedronate is conditionally recommended over placebo in children and adolescents on chronic oral GC treatment, diagnosed with osteoporosis.

Further investigations on risedronate for GIOP are required. A study demonstrated an increase in lumbar spine BMD in patients treated with CG.[40] As mentioned above, in patients who already have a fracture, IV bisphosphonates are preferred; oral bisphosphonates are an option in cases of non-availability.

Recommendation 6. Pamidronate is conditionally recommended over calcium and vitamin D only in children and adolescents on chronic oral GC treatment, diagnosed with osteoporosis.

Few data are currently available on bisphosphonates and their use in pediatrics, and even less on IV bisphosphonate use in this population. Most of the experience regarding the safety and effectiveness of pamidronate has been reported in patients with osteogenesis imperfecta. Glorieux et al. reported that the bone mass of pediatric patients with osteogenesis imperfecta increased significantly with IV pamidronate, with no negative effects on growth.[41] Due to the low/moderate quality of the evidence of published studies, the administration of pamidronate is recommended in the study population with osteoporosis and on GC therapy.

Recommendation 7. Zoledronic acid is suggested over placebo in children and adolescents on chronic oral GC treatment, diagnosed with osteoporosis.

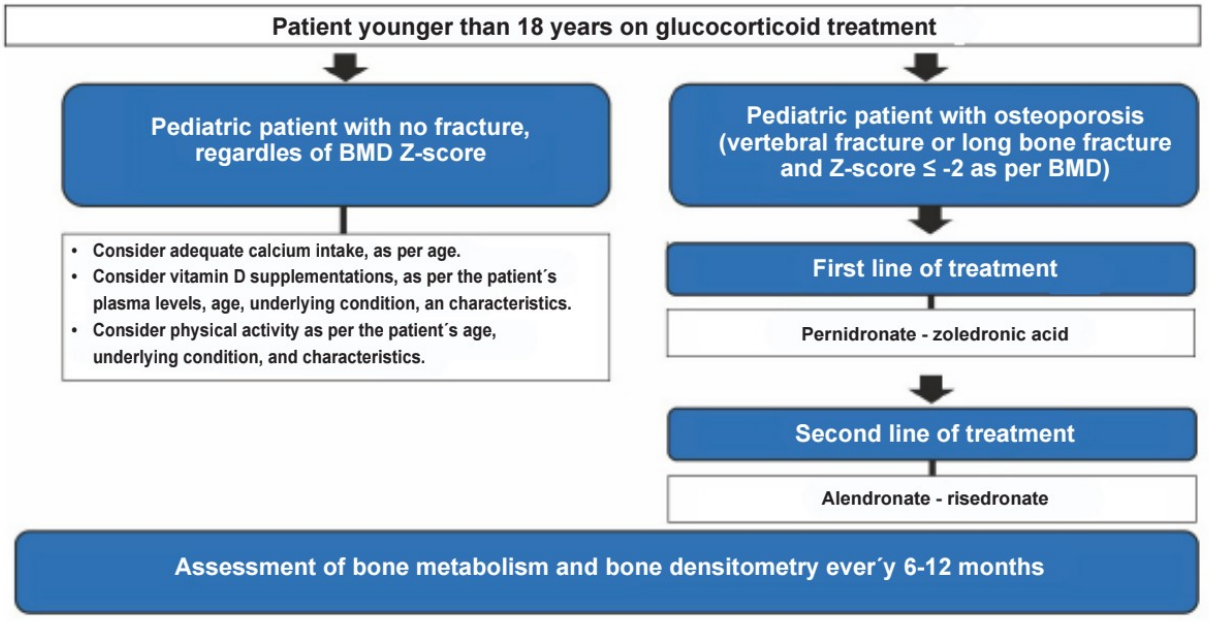
No studies have been conducted in pediatric patients with GIOP and fractures and treatment with zoledronic acid. The pediatric experience with zoledronic acid is based mainly on its use in patients with osteogenesis imperfecta versus other bisphosphonates[44–46] and on retrospective studies,[47,48] both in children and adults with osteogenesis imperfecta, and it has demonstrated to reduce osteoporotic fractures. For this reason, the expert panel suggests using zoledronic acid in patients with fractures.

Figure 1 shows the prevention and treatment algorithm recommended for the pediatric population.

DISCUSSION

GCs are used in a wide variety of diseases in children and adolescents, and several studies have shown adverse effects on bone mass and growth.[49] GIOP is a condition that causes important alterations in the quality of life; the clinical condition represents the effect of the underlying disease in addition to the direct and

Figure 1. Patient younger than 18 years on glucocorticoid treatment



indirect harmful effects of GC on the skeleton. We believe that prospective, controlled studies are required to assess the results of prevention and osteoactive treatment in children and adolescents receiving chronic GC treatment. The basis of current treatment is the prevention of bone involvement and ensuring that the patient achieves adequate levels of daily calcium intake, vitamin D supplementation, and physical activity, all in the context of adequate clinical management of the patient's baseline condition and a rational use of GC. In addition, it is worth noting the importance of systematic monitoring of bone health in this population through the use of imaging techniques and lab test controls. The latter allows to detect and characterize bone involvement early and, at the same time, establish therapeutic measures aimed at improving it.

In cases of established osteoporosis, i.e. patients with the presence of brittle fractures, IV bisphosphonates are the medication of choice for treatment. It is critical to limit the long-term use of GC to the minimum effective dose and the shortest duration possible.

CONCLUSIONS

These recommendations provide guidance for physicians who must make decisions for pediatric patients on GC therapy. ■

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Supplementary material available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2024/2948_AE_Brunetto_Anexo.pdf

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