
بسم الله النور

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Glucocorticoid induced osteoporosis in Children&Adolescent

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- Most of the underlying diseases carry an increased risk of skeletal fragility, particularly inflammatory disorders and hematological malignancies
- use of GC, in children can lead to decreased BMD ,and increased risk of vertebral fractures.

Factors affecting on bone fragility

- **Cumulative dose** of systemic GCs, and **treatment duration** are the two main determinants of impact on bone strength
- **High dose GCs** predispose to increased bone fragility.
- **Low to medium doses** can also cause detrimental effects on bone, but evidence in children is inconclusive

Definitions of Low, Medium, and High Doses of Prednisolone in Children

- **Low Dose:** Less than 0.5 mg /kg/day
- **Medium Dose:** Between 0.5 to 1 mg /kg/day
- **High Dose:** Greater than 1 mg /kg/day

In adult

- Mild:< 7.5 mg/ day
- Moderate 7.5–14.9 mg/day
- High ≥ 15 mg/ day
- Very high ≥ 30 mg/ day

Definition of osteoporosis

In children with **known risk factors** for either

- **primary osteoporosis such as OI**
- **Or secondary osteoporosis due to** long term high dose glucocorticoids, chronic neuromuscular disorders

- The presence of a single **low-trauma** fracture warrants a diagnosis of osteoporosis .

Definition of low trauma

The 2013 ISCD criteria defined low-trauma

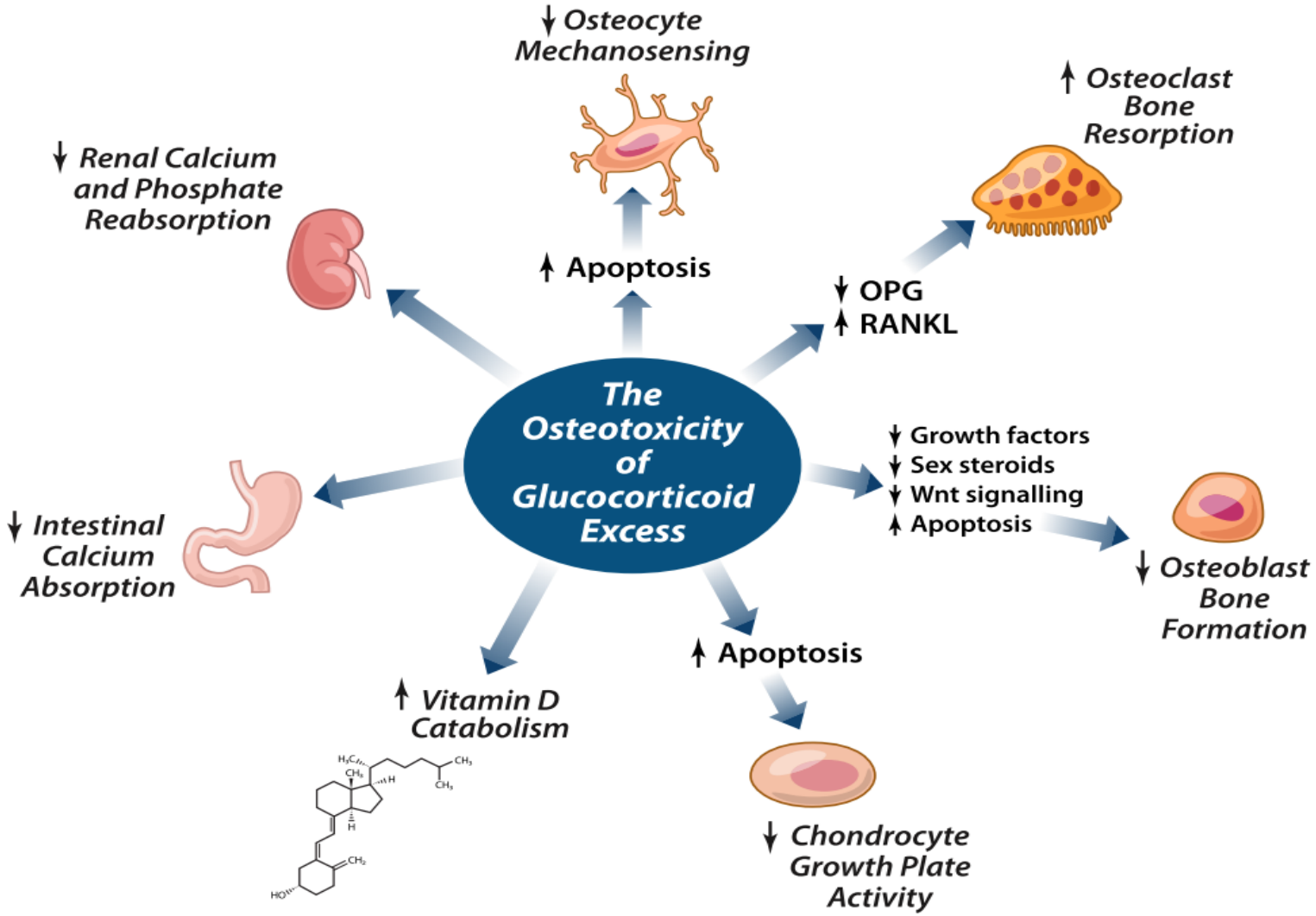
- **Falling from** a height of 0.5 meters or less on the ground
- **Falling from** a standing height or less, at no more than walking speed
- **Falling from** a height of 0.5 to 3 meters on a flexible surface

Glucocorticoid induce osteoporosis

Decreased bone formation

- inhibition of osteoblast proliferation and differentiation
- Reduce marrow cell osteoblast differentiation
- Promote **osteoblast apoptosis**
- Antagonize the anabolic action of PTH
- Inhibit production of IGF-1 and testosterone
- Decreased serum and urine biochemical markers of bone formation

Glucocorticoid induce osteoporosis



How long corticosteroids intake increase risk of osteoporosis?

- Any patient taking **any dose of** glucocorticoid with an anticipated duration of ≥3 months requires an evaluation

- Patients treated with systemic GCs, **lose bone mass more** markedly during the **first 3–6 months of treatment**, mainly **trabecular bone**

What dose of corticosteroids increase the risk of osteoporosis?

The Spanish Rheumatology Society Consensus holds

- **5 mg/day of prednisone** for more than **three months**
- Fracture risk have been reported to persist with prednisone **doses of 2. 5 a 7. 5 mg/ day**
- **Chronic GC at a dose of ≥0.1 mg/kg/day> 3 month**

What dose of corticosteroids increase the risk of fracture ?

- GC doses **≥2.5 mg/day** increase fracture at both the **spine and hip**
- GC**<2.5mg/day** increase the risk of **spinal fracture**
- Every **0.5-mg/kg** increase in the average **daily GC dose** was associated with a 2-fold increased risk of **fracture** among children with rheumatic disorder

What dose of cumulative GCs increase risk of osteoporosis?

- **CD** was categorized as
- **low < 1 g CD**
- **High ≥ 1 g CD**
- **Every 1 g** /M2 **increase** in cumulative GC exposure
  in the first 5 weeks of GC exposure
- **lumbar BMD Z-scores** were lower by **0.37**
  in children with nephrotic syndrome

A systematic review and meta-analysis of glucocorticoid-induced osteoporosis in children

In summary, two studies of **high-dose short-duration (≤ 3 months)** glucocorticoid therapy demonstrated declines in spine BMD, whereas a 52-week study reported a significant increase in spine BMD despite low-dose glucocorticoid therapy

Higher mean daily prednisolone dose (0.62 mg/kg versus 0.27 mg/kg, $p < 0.01$) but not a higher cumulative dose, compared to children without fracture. Authors noted a **correlation between the mean daily prednisolone dose** and the time to first vertebral fracture ($r = -0.67$, $p < 0.001$)

Glucocorticoid therapy induce lower spine BMD and higher rates of morphometric fractures compared to healthy children

Semin Arthritis Rheum. 2014 Feb

Glucocorticoid &Vertebral fractures

- vertebral fractures are more frequent in **GC-treated children** than nonvertebral fractures
- Incidence rate of VF **around 10% during the first year**, with nearly 50% of such cases being asymptomatic

.**6 years following GC initiation:**

vertebral fractures occurred in

- 30%of children with leukemia
- 16% of children with rheumatic conditions
- up to 75% of boys with GC-treated DMD

Glucocorticoid &Vertebral fractures

- **Vertebral fractures** have been diagnosed as early as 4 to 6 months following GC initiation in children with GC-treated inflammatory disorders and DMD
- **peak vertebral fracture** incidence in childhood leukemia and rheumatic conditions occurs at 12 months following GC initiation
- Even GC treated-children with normal DXA results can suffer vertebral fractures

Vertebral fractures prevention

- **It is recommended** in addition to DXA
- **To perform** simple lateral thoracic and lumbar X-rays to assess VF
- Every 6 months to 2 years (with 1 year being the average),

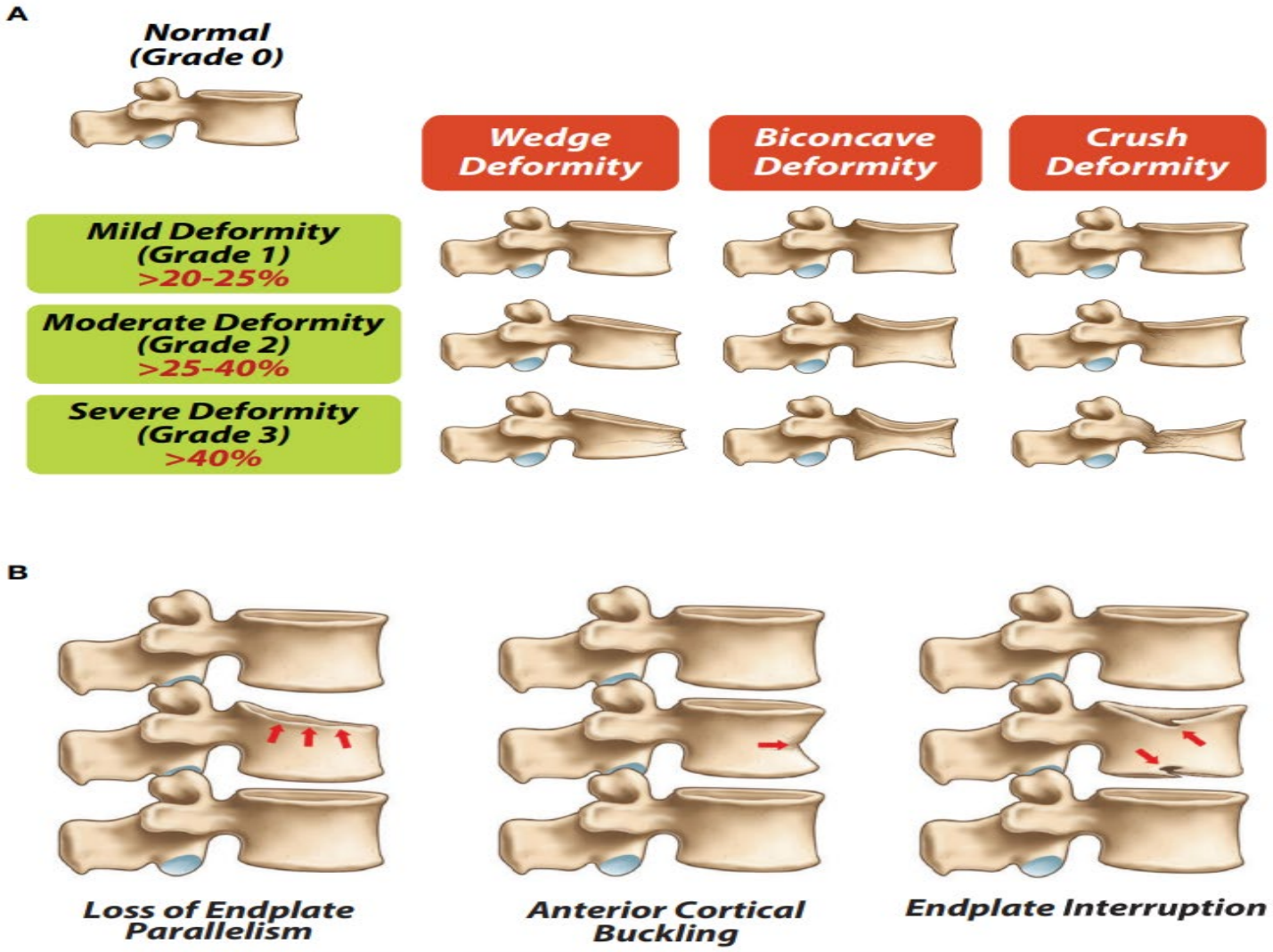
Asymptomatic Vertebral fractures

- Asymptomatic vertebral fractures are associated with an increased risk of future vertebral fractures
- Asymptomatic VF particularly can present with **back pain**
- **when left untreated**, may progress to more advanced collapse in those with persistent risk factors

Data have shown that fracture risk can persist up to 1 year after oral glucocorticoid cessation

GCs are potent disruptors of bone strength

Early signs of vertebral fracture



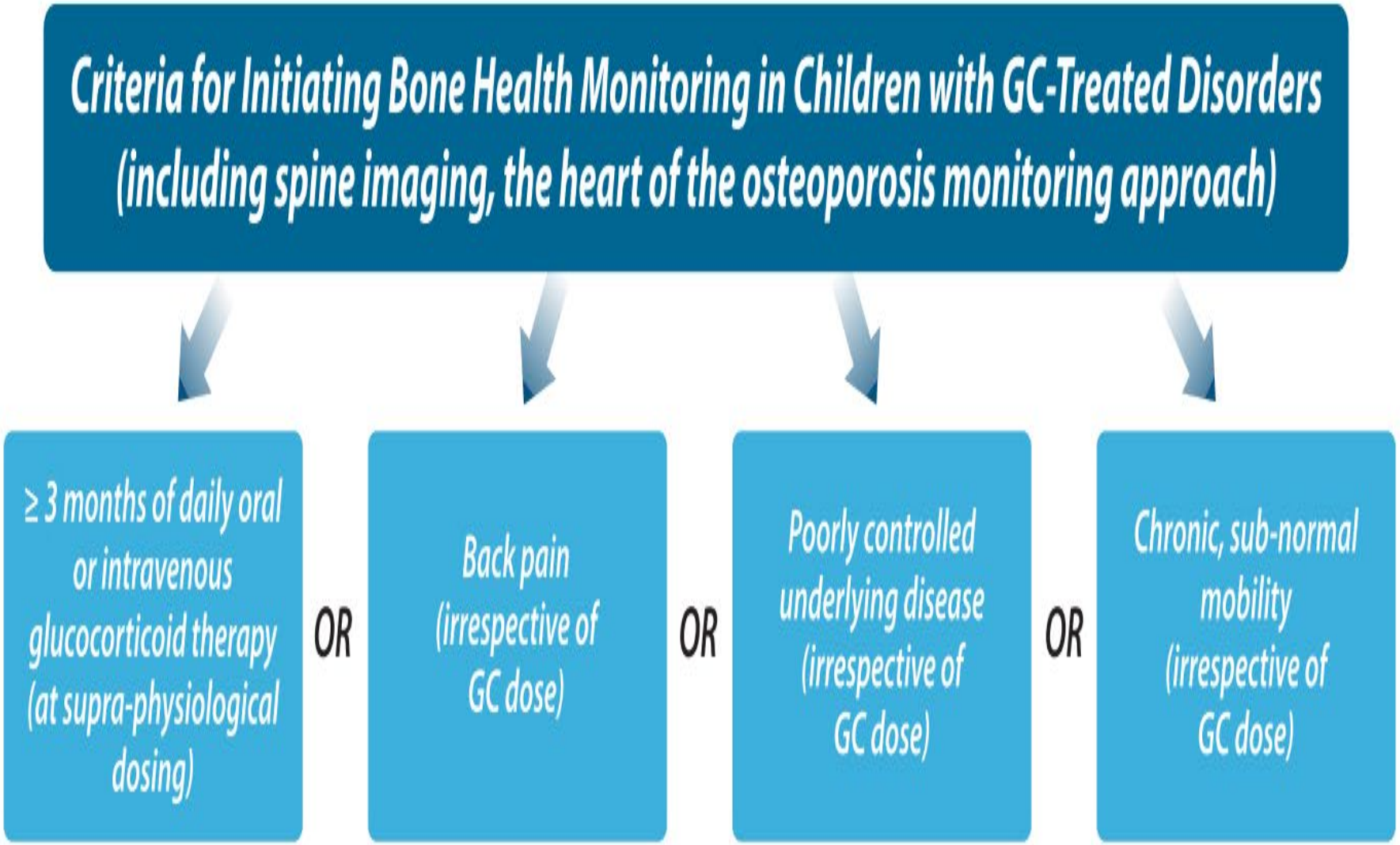
Early signs of vertebral fracture

STOPP Consortium

- **Normal <20%**
- **Grade 1 (mild) >20 to ≤25%,**
- **Grade 2 (moderate) >25% to ≤40%**
- **Grade 3 (severe) >40%**

Bone health monitoring

A


Criteria for Initiating Bone Health Monitoring in Children with GC-Treated Disorders (including spine imaging, the heart of the osteoporosis monitoring approach)
≥ 3 months of daily oral or intravenous glucocorticoid therapy (at supra-physiological dosing)
OR
Back pain (irrespective of GC dose)
OR
Poorly controlled underlying disease (irrespective of GC dose)
OR
Chronic, sub-normal mobility (irrespective of GC dose)

osteoporotic event&Bone health monitoring

- initiate bone health monitoring in children is triggered by ≥3 months
- Daily oral, or intermittent IV
- At supraphysiological doses
- Hydrocortisone or equivalent > 8-10mg/M2/day

Approach to the Monitoring and Diagnosis of Osteoporosis in Children with GC-Treated Disorders After the Decision to Monitor the At-Risk Child has been Made

Rule out a disorder of mineral ion metabolism (e.g. rickets, vitamin D deficiency)
Assess dietary intake, supplement use, celiac disease, serum and urine calcium & phosphate, serum and urine creatinine, parathyroid hormone, alkaline phosphatase, 25-hydroxyvitamin D, $1,25(OH)_2D_3$, x-rays for rickets.

Disorder of mineral metabolism suspected:
Pursue further testing/ treatment as needed

- Lateral spine imaging* at baseline and annually
- Monitor changes in body mass index (BMI) every three to six months
- BMD at baseline and annually
- Consider a BMD sooner (at six months), if the patient develops Cushingoid features, including increases in BMI Z-scores
- Consider lateral spine imaging sooner if:

Back pain
OR
≥ 0.5 decline in LS BMD Z-scores on two consecutive measurements

Early signs of vertebral fracture
(> 20% loss of vertebral height ratio, loss of endplate parallelism, endplate interruption, anterior cortical buckling)
OR
Low-trauma** long bone fracture

the GC treated or previously treated child meets criteria for Osteoporosis

YES

Optimal timing for follow-up studies

- Lateral spine x-ray is recommended in order to detect VF at **the beginning of treatment with GCs and an annual or biannual**
- since **fracture** are frequently **asymptomatic** and can appear even in patients **with Z-scores higher than -2**
- It is recommended to carry out **lumbar spine or TBLH DXA** within the **first six months** after the beginning of treatment with GCs, and then **every 9 to 12 months if treatment continues**

spontaneous recovery osteoprosis

- **Once the diagnosis of osteoporosis has been made**, the next step is to determine whether the patient has the potential to undergo spontaneous recovery
- **medication-unassisted** recovery from bone fragility.
- **The juvenile skeleton** has potential to recover from osteoporosis,

spontaneous recovery osteoprosis

- There is sufficient residual growth potential to permit adequate bone mineral accretion for full recovery.
- **Recovery from osteoporosis** does not only involve reclamation of BMD; restoration of normal vertebral dimensions **(and thereby total spinal height)**

is also a key index of recovery

persistent vertebral deformity

A recent study by the STOPP Consortium found in GC-treated children with

- leukemia, nephrotic syndrome, and rheumatic conditions that patients with
- **Higher GC exposure**
- **Higher SDI**
- **More severe fractures**
- **lumbar vertebral fractures**

were at increased risk for persistent vertebral deformity

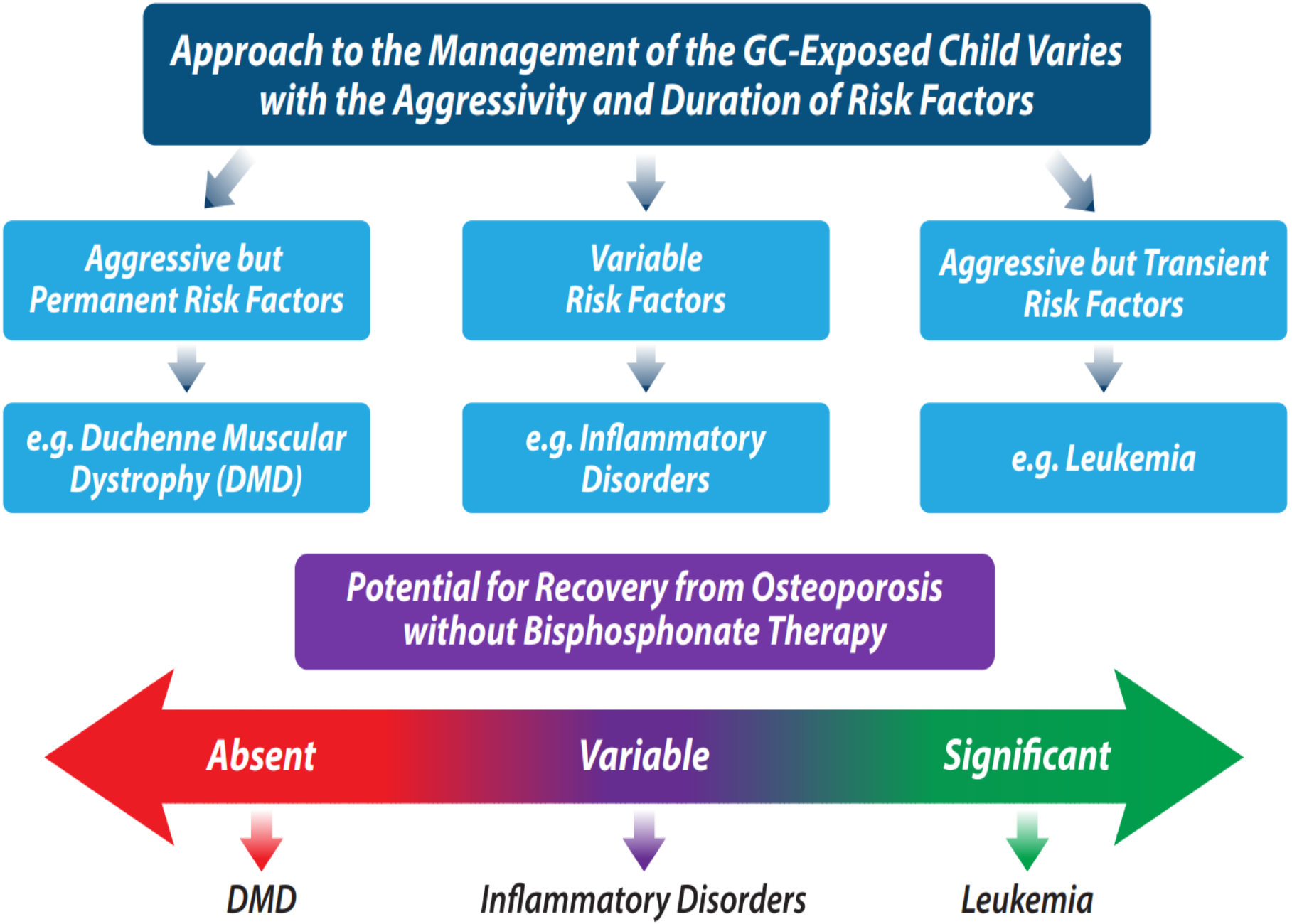
- **SDI= spinal deformity index**

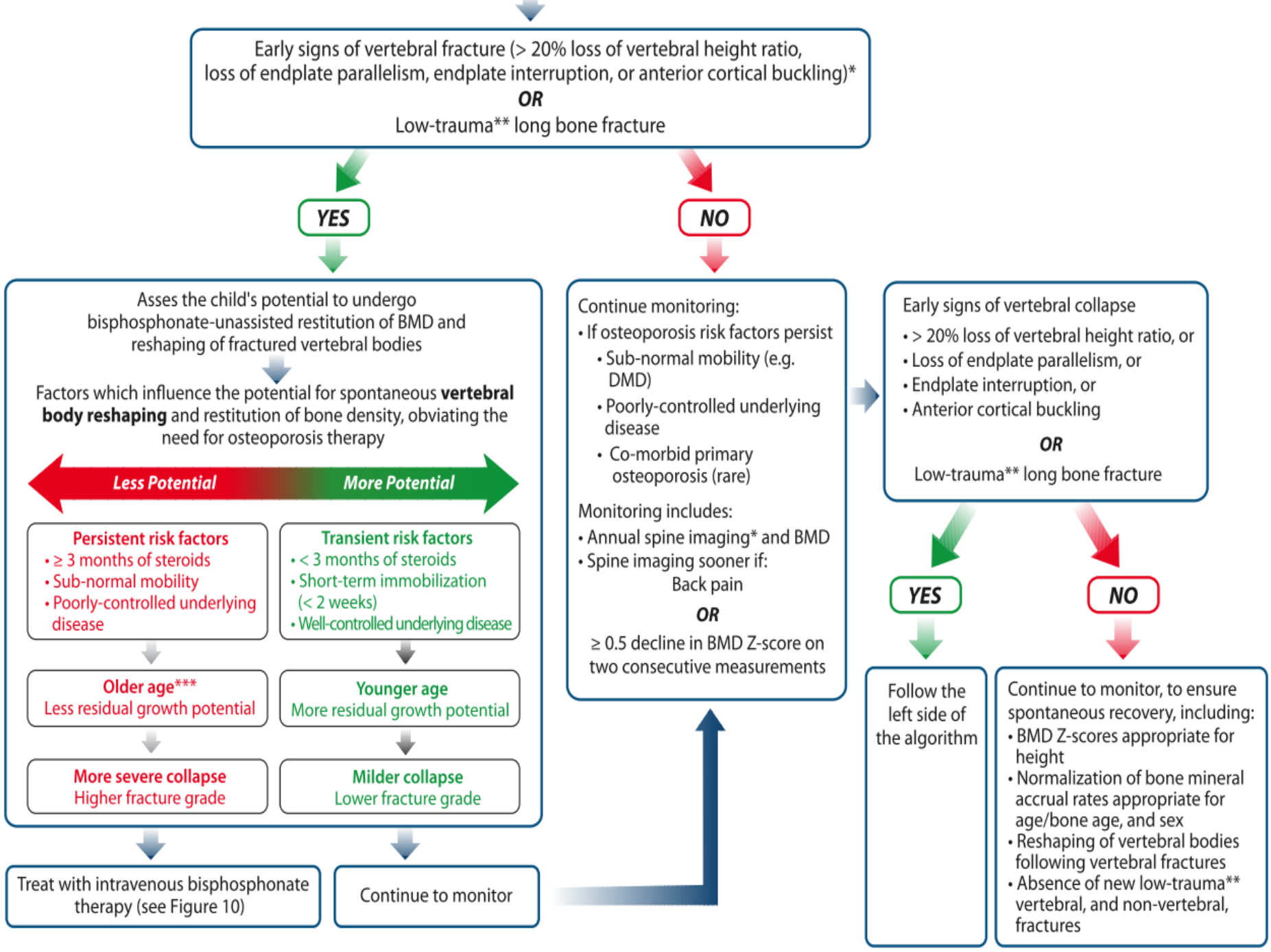
Steps to gauge

The child's ability to undergo spontaneous (bisphosphonate unassisted) restitution of normal vertebral dimensions following vertebral fractures and reclamation of bone mineral density

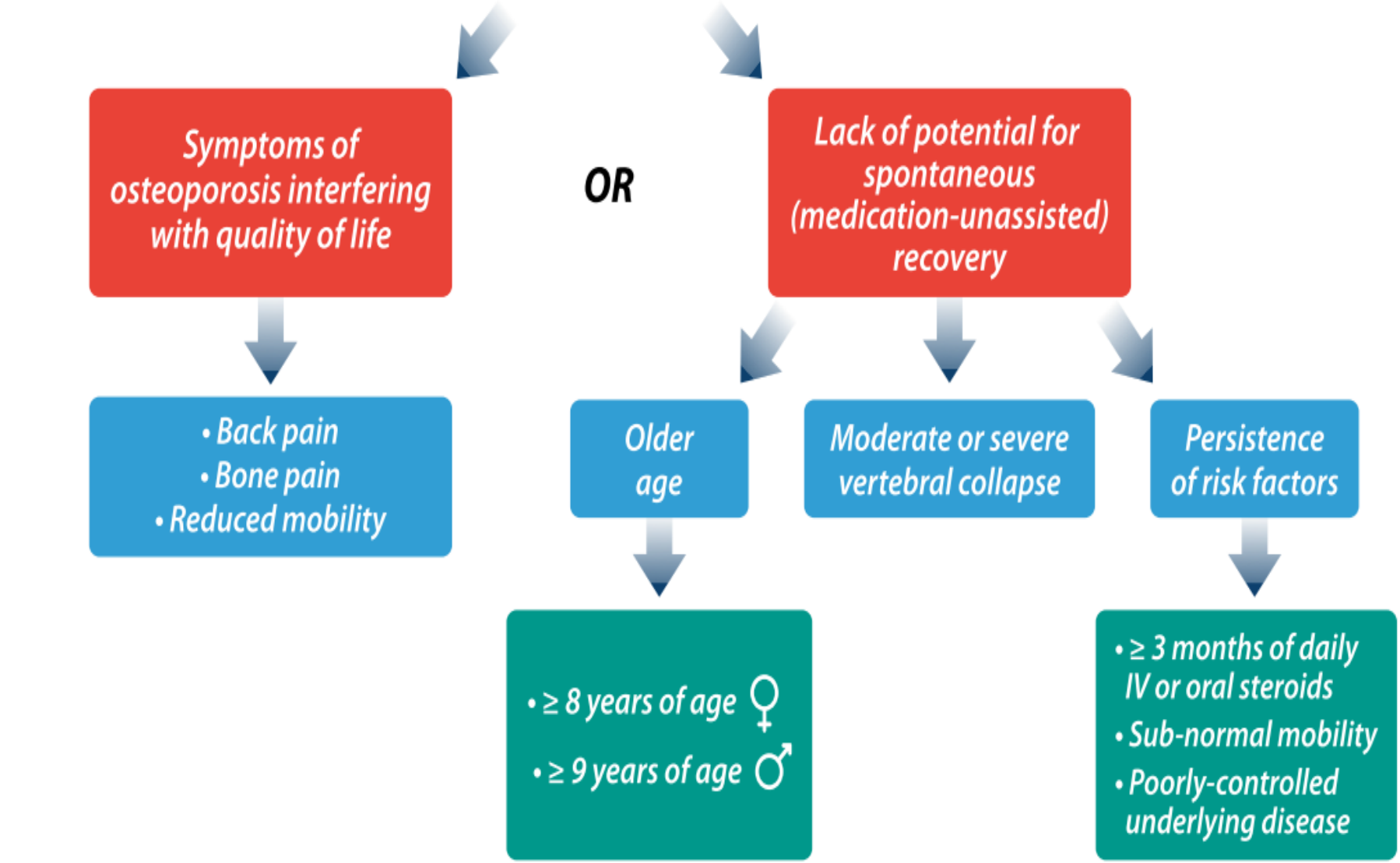
The decision to treat or non treat osteoporosis

- The decision to treat a child with a bisphosphonate or not determines the nature and frequency of follow-up


Approach to the Management of the GC-Exposed Child Varies with the Aggressivity and Duration of Risk Factors
Aggressive but Permanent Risk Factors
Variable Risk Factors
Aggressive but Transient Risk Factors
e.g. Duchenne Muscular Dystrophy (DMD)
e.g. Inflammatory Disorders
e.g. Leukemia
Potential for Recovery from Osteoporosis without Bisphosphonate Therapy
Absent
Variable
Significant
DMD
Inflammatory Disorders
Leukemia


Early signs of vertebral fracture (> 20% loss of vertebral height ratio, loss of endplate parallelism, endplate interruption, or anterior cortical buckling)*
OR
Low-trauma** long bone fracture
YES
NO
Asses the child's potential to undergo bisphosphonate-unassisted restitution of BMD and reshaping of fractured vertebral bodies
Factors which influence the potential for spontaneous vertebral body reshaping and restitution of bone density, obviating the need for osteoporosis therapy
Less Potential
More Potential
Persistent risk factors
• ≥ 3 months of steroids
• Sub-normal mobility
• Poorly-controlled underlying disease
Transient risk factors
• < 3 months of steroids
• Short-term immobilization (< 2 weeks)
• Well-controlled underlying disease
Older age***
Less residual growth potential
Younger age
More residual growth potential
More severe collapse
Higher fracture grade
Milder collapse
Lower fracture grade
Treat with intravenous bisphosphonate therapy (see Figure 10)
Continue to monitor
Continue monitoring:
• If osteoporosis risk factors persist
• Sub-normal mobility (e.g. DMD)
• Poorly-controlled underlying disease
• Co-morbid primary osteoporosis (rare)
Monitoring includes:
• Annual spine imaging* and BMD
• Spine imaging sooner if:
Back pain
OR
≥ 0.5 decline in BMD Z-score on two consecutive measurements
Early signs of vertebral collapse
• > 20% loss of vertebral height ratio, or
• Loss of endplate parallelism, or
• Endplate interruption, or
• Anterior cortical buckling
OR
Low-trauma** long bone fracture
YES
NO
Follow the left side of the algorithm
Continue to monitor, to ensure spontaneous recovery, including:
• BMD Z-scores appropriate for height
• Normalization of bone mineral accrual rates appropriate for age/bone age, and sex
• Reshaping of vertebral bodies following vertebral fractures
• Absence of new low-trauma** vertebral, and non-vertebral, fractures

Summary of the Main Factors in the Decision to Treat with Bisphosphonate Therapy Following a Fragility Fracture in GC-Treated (or Previously GC-Treated) Children



The Treatment of Bone Fragility in Children with Glucocorticoid-Induced Osteoporosis

Less potential for spontaneous recovery (see Figures 9a,b)

- Older age (≥ 8 years in girls or ≥ 9 years of age in boys), irrespective of ongoing risk factors

OR

- Younger age, but persistence of risk factors, including:
  - Ongoing glucocorticoid exposure
  - Sub-normal mobility
  - Poorly-controlled underlying disease

Intravenous bisphosphonate therapy may still be indicated in younger children with bone fragility and potential for recovery, if the fractures significantly impact the young child's quality of life (e.g. back pain due to vertebral fractures interfering with sleep, school and/or play)

Start intravenous bisphosphonate therapy at published, initiation doses* for children with:

≥ 1 low trauma vertebral fracture or ≥ 1 low trauma long bone fracture

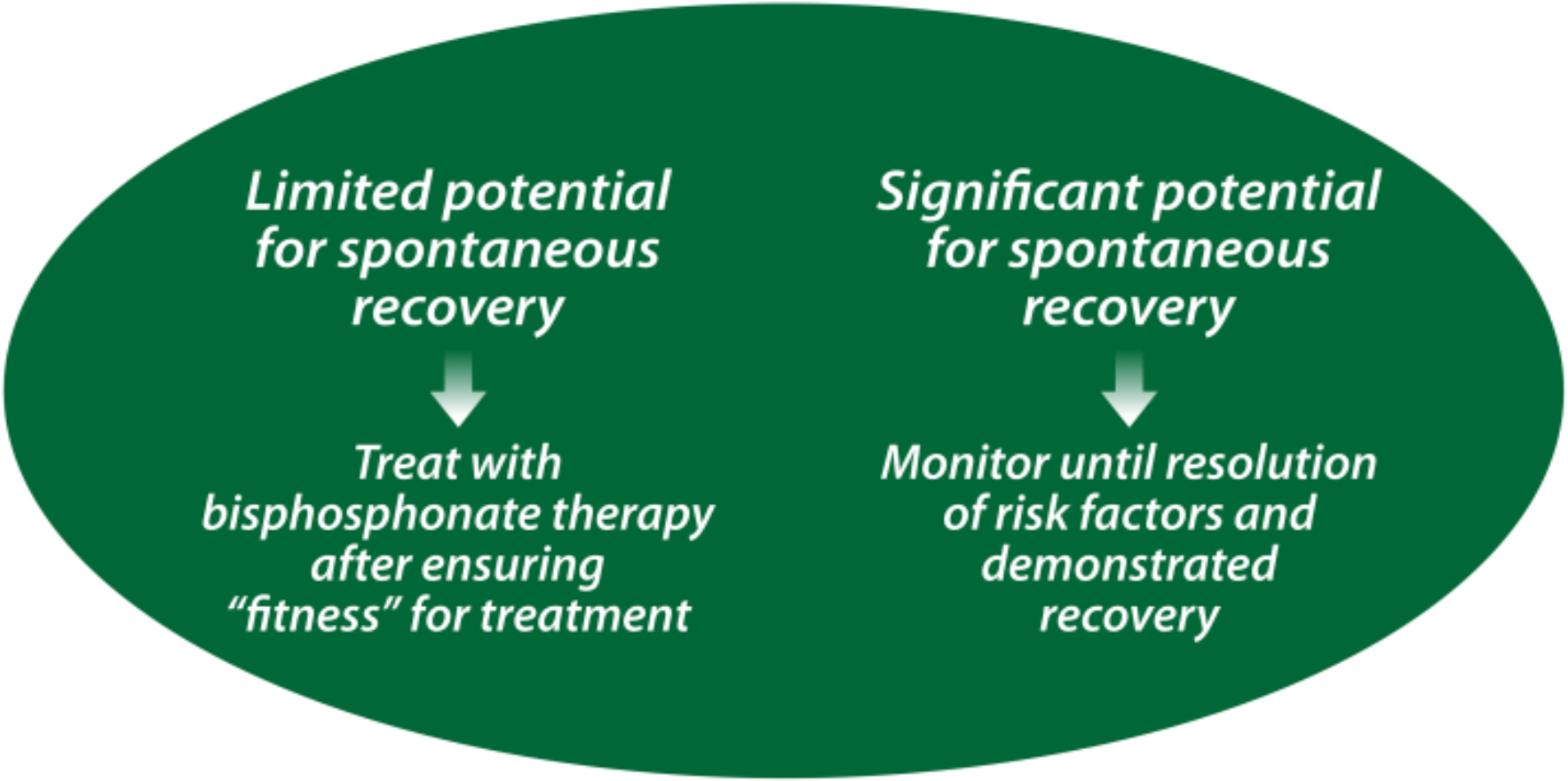

Limited potential for spontaneous recovery
Treat with bisphosphonate therapy after ensuring "fitness" for treatment
Significant potential for spontaneous recovery
Monitor until resolution of risk factors and demonstrated recovery

FIGURE 9

Treatment of osteoporosis in children

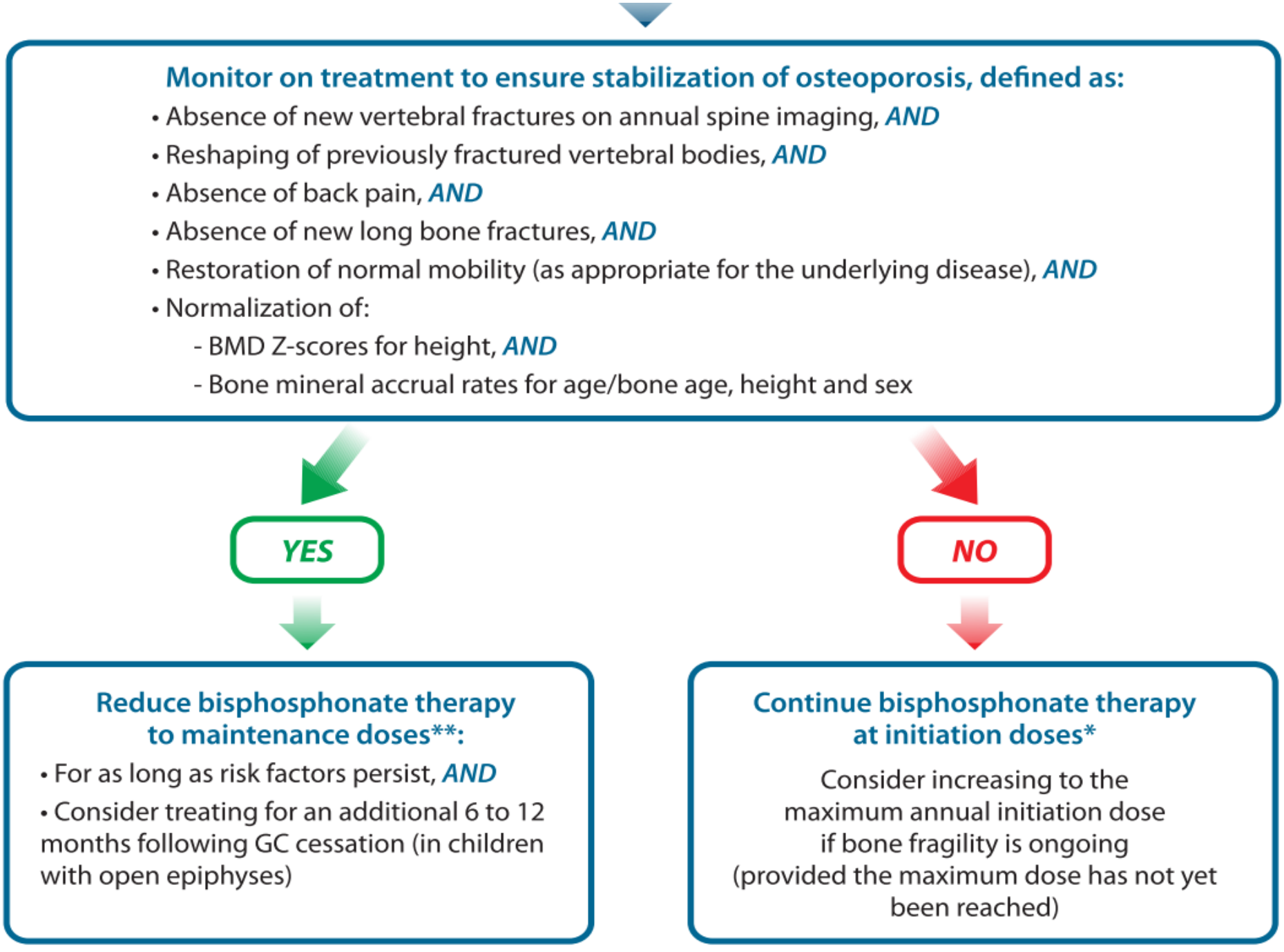
- **Children ages** 4-17 years with **an osteoporotic fracture** who are continuing treatment with
- GCs at a dose of ≥0.1 mg/kg/day for >3 months (high risk)
- We conditionally recommend treating with an oral or IV BP.

- **American college rheumatology 2023**

Treatment of osteoporosis in children

- **Children ages** 4–17 years treated with GCs for >3 months low and moderate risk
- We conditionally recommend optimization of dietary and supplementation of calcium and vitamin D
- We recommend against starting oral or IV BP due to low risk of OP fractures in this age group.

- **American college rheumatology 2023**


Monitor on treatment to ensure stabilization of osteoporosis, defined as:
• Absence of new vertebral fractures on annual spine imaging, AND
• Reshaping of previously fractured vertebral bodies, AND
• Absence of back pain, AND
• Absence of new long bone fractures, AND
• Restoration of normal mobility (as appropriate for the underlying disease), AND
• Normalization of:
- BMD Z-scores for height, AND
- Bone mineral accrual rates for age/bone age, height and sex
YES
NO
Reduce bisphosphonate therapy to maintenance doses**:
• For as long as risk factors persist, AND
• Consider treating for an additional 6 to 12 months following GC cessation (in children with open epiphyses)
Continue bisphosphonate therapy at initiation doses*
Consider increasing to the maximum annual initiation dose if bone fragility is ongoing (provided the maximum dose has not yet been reached)

Bisphosphonate therapy in children with low BMD

Treatment for children with low BMD without osteoporosis
Tanner 2 puberty

- **When active** risk factors are present:
- patients with **Z ≤ − 2. 5 SD** with a declining trajectory confirmed at least on two separate occasions with one year apart
- **When no active** risk factors:
- patients with Z ≤ -3DS with a declining trajectory confirmed on at least on two separate occasions with one year apart

Misinterpretation of BMD

Over the last decade or so

- The pGIO field has moved away from a BMD-centric toward a fracture-focused approach to the diagnosis
- BMD a surrogate for **bone strength**
- BMD can be low due to **short stature**
- **Z-scores can decline due to** poor linear height velocity, weight loss, or delayed puberty.

Preventive actions& Follow-up

American College of Rheumatology

- prescribing the lowest possible dose of GCs to control the underlying disease
- To encouraging physical exercise
- Avoiding toxic products, such as tobacco and alcohol

Preventive actions& Follow-up

GIOP

- Children beginning or continuing chronic GC at a dose of ≥2.5 mg/day for >3 months,
- Recommends maintaining calcium and vitamin D supplementation **for three months after discontinuation of GCs treatment** since its effect on bone continues even after treatment has be same dose recommended

Adrenal insufficiency

- The first infusion side effects of IV bisphosphonate therapy can precipitate adrenal insufficiency in patients on **chronic GC therapy**,
- To recommend steroid stress dosing following the first dose of IV bisphosphonates in patients on chronic GC therapy, either prophylactically or upon developing symptoms that would normally prompt such intervention fever, vomiting

Special Considerations in Children at the Extreme Ends of Potential for Recovery From GIO

inhaled GCs & osteoporosis

- Children receiving budesonide for **3–6 y** did not show differences in BMD compared with control children
- A decade later, the same authors reported that treatment with BUD at a mean daily dose of 350 µg for a mean of 14 y **did not adversely** affect BMD in adulthood in these children with asthma
- The dose higher than the **equivalent of 800 mcg/day** of budesonide associated with an accelerated decrease in BMD and a higher risk of fractures

inhaled GCs & osteoporosis

- **49 children** treated with **beclomethasone dipropionate** or DSCG for 7 month
- Bone mass was found **not to have changed** after either treatment within or between the groups.

Association between ICS use and fracture risk in children with asthma

- A systematic review and meta-analysis reported a lack of **convincing evidence** for an association
- A study in the United Kingdom in 2004 compared fracture risk in children receiving different types of GCs and **found a greater risk of fracture in the ICS group**
- . Conversely, another United Kingdom study in 2004 **did not find** a significant association between fractures and current use of ICSs in children.
- Studies on the association between ICS use and reduced bone mineral density, a risk factor for fracture, also present **conflicting results**.
-

inhaled GCs & fracture

- The largest prospective study on ICSs and fracture in children aged 4 to 17 years
- 18% increased risk of fracture for children
- **The authors hypothesized** that greater disease severity would reduce a child's physical activity level, decreasing bone strength and predisposing a child for fracture
- *research output: Contribution to journal › Article › peer-review*

Assesment of patients on inhaled GCs

- **it is not advisable to** routinely carry out such procedures as **lateral spine x-rays or DXAs**, unless these patients have other risk factors

Preventive actions for inhaled GCs

- Role of calcium and vitamin D supplementation **has not yet been established**
- Although some groups recommend supplementation for higher risk populations

leukemia &Vertebral fractures

In childhood ALL

16% are reported to have a **symptomatic/asymptomatic vertebral** fracture at the time of diagnosis, and the incidence increases further, especially during periods of high glucocorticoid exposure

- Genant-defined vertebral fractures at diagnosis were a strong predictor of new vertebral and long bone fractures over the ensuing 5 years

leukemia &Vertebral fractures

- Most children with leukemia appear to have the potential to undergo **vertebral body reshaping to** reclaim normal vertebral dimensions over time, except for older adolescents and those with more severe vertebral collapse

Follow up leukemic patients

- IGHG in 2021 recommends baseline DXA between 2-5 years after completing cancer treatment, and again at 25 years of age when bone mass peaks, or earlier depending on risk factors
- Other international guidelines recommend carrying out a BMD at the end of leukemia therapy
- and if >1.0 SD for age and sex, to repeat the measurement at age 25

longitudinal STOPP study

- **80% of the children with leukemia & vertebral fractures** underwent complete vertebral body reshaping over 6 years following diagnosis
- while the remainder underwent **partial 15%**
- or absent 5% reshaping
- **The intermittent nature of GC therapy** in this setting combined with the typically young age in the majority at diagnosis are proposed to be important drivers of the recovery phenotype.

Follow up leukemic patients

- **Questions remain** about the treatment approach in those with **residual low BMD at the end of growth**
- **showing an increased frequency of nondigital fractures**

Follow up leukemic patients

- It is presently unknown whether a course of oral or IV bisphosphonate therapy in those with **residual BMD deficits** following completion of therapy will reduce the known fracture risk
- This is an important research question going forward

Increased Prevalence of Fractures in Congenital Adrenal Hyperplasia: A Swedish Population-based National Cohort Study

Patients with CAH (n = 714, all 21OHdeficiency were compared with controls
Result: Mean age was 29.8 ± 18.4 years. Individuals with CAH had more fractures compared to controls [23.5% vs 16.1%, odds ratio (OR) 1.61,
The highest prevalence of fractures was seen in **SV phenotype&I172N genotype**
It should be noted that the average age was only **around 30 years**, and most osteoporotic fractures occur in older age
Supraphysiological glucocorticoid replacement dosing in combination with low androgen concentrations is the most probable cause for the increased risk of fracture
Glucocorticoid therapy should be optimized, together with lifestyle interventions, to improve bone health

The Journal of Clinical Endocrinology & Metabolism, 2022

BioMed Research International

Forward Series

Review Article | Open Access

Glucocorticoid-Induced Osteoporosis in Children with 21-Hydroxylase Deficiency

authors concluded that the CAH patients treated for many years had predominantly low bone formation but also unexplained low bone resorption

Despite the conflicting results in the literature about the bone status on GC-treated patients with 21-OHD, many reports consider these subjects to be at risk for osteoporosis and fractures.

it should be a useful monitoring bone status in treated 21-OHD children, checking BMD and bone turnover markers, in order to avoid GIO in adulthood.

DMD& osteoporosis

- an absence of evidence for spontaneous vertebral body reshaping or reclamation of BMD
- Even with early bisphosphonate treatment**, bone health deficits persist and progressive vertebral collapse**
- . This structural aberrancy is unchanged on bisphosphonate therapy

DMD& osteoporosis

Current guidelines advocate for

- continuing bisphosphonate treatment in patients receiving ongoing GC therapy who exhibit moderate to high risk of fracture
- **In DMD**, the permanency and high-risk nature of osteoporosis risk factors, including
- progressive myopathy, loss of ambulation, and high-dose GC therapy,

DMD& osteoporosis

- .There are no studies that have formally assessed the risks and benefits of continuing bisphosphonate therapy postepiphyseal fusion among individuals with DMD **who initiated therapy in childhood**.

How long should bisphosphonates be administered?

- Bisphosphonates are typically administered for **2 to 5 years** in pediatric patients with secondary osteoporosis, depending on the severity of bone density loss and the patient's response to treatment.
- Treating for an additional **6-12 months** following GC cessation in children with open epiphyses
- Fracture free for at least 6 -12 months following resolution of risk factors
- Bone mineral accrual Z-score trajectory has also normalize

Discontinuation Criteria

- **Improved Bone Mineral Density (BMD)** based on height
- **Stabilization of Bone Turnover Markers:** Normalization of serum calcium, phosphate, and bone turnover markers.
- **Clinical Improvement:** Reduction in pain and functional improvement.

Discontinuation Criteria

- The patient should be Fx free for 6 to 12 months
- The previous vertebral fracture should be stable or under reshape
- **Ongoing Monitoring:**
- After discontinuation, regular monitoring with DEXA scans (every 6–12 months) and biochemical markers is necessary to ensure sustained bone health

Special Considerations

- If the patient remains at high risk of fractures or if new fractures occur during therapy
- Treatment duration may be extended beyond 5 years.

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