Approach to the Pediatric Patient with Glucocorticoid-Induced Osteoporosis

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Abbreviations:

a = areal; BA = bone age; BMD = bone mineral density; BMI = body mass index; CA = chronological age; CSA = cross-sectional area; DMD = Duchenne muscular dystrophy; DXA = dual-energy x-ray absorptiometry; HCE = hydrocortisone equivalents; GC = glucocorticoid(s); GIO = Glucocorticoid-induced osteoporosis; GH = growth hormone; IV = intravenous; JDM = juvenile dermatomyositis; rhGH = recombinant human growth hormone; LS = lumbar spine;
25OHD = 25-hydroxyvitamin; OI = osteogenesis imperfect; pGIO = pediatric glucocorticoid-induced osteoporosis; pQCT = peripheral quantitative computed tomography; SDI = Spinal Deformity Index; sJIA = systemic juvenile idiopathic arthritis; STOPP = Canadian STeroid-induced Osteoporosis in the Pediatric Population; TBLH = total body less head; v = volumetric; VFA = vertebral fracture assessment; ZA = zoledronic acid.

Keywords: glucocorticoids, children, osteoporosis, fractures, bone mineral density, treatment

Running title: Management of Pediatric Glucocorticoid-Induced Osteoporosis

Abstract

Glucocorticoid (GC) therapy remains the cornerstone of treatment for many conditions of childhood and an important cause of skeletal and endocrine morbidity. Here, we discuss cases that bring to life the most important concepts in the management of pediatric GC-induced osteoporosis (pGIO). Given the wide variety of underlying conditions linked to pGIO, we focus on the fundamental clinical-biological principles that provide a blueprint for management in any clinical context. In so doing, we underscore the importance of longitudinal vertebral fracture phenotyping, how knowledge about the timing and risk of fractures influences monitoring, the role of bone mineral density in pGIO assessments, and the impact of growth-mediated "vertebral body reshaping" after spine fractures on the therapeutic approach. Overall, pGIO management is predicated upon early identification of fractures (including vertebral) in those at risk, and timely intervention when there is limited potential for spontaneous recovery. Even a single, low-trauma long bone or vertebral fracture can signal an osteoporotic event in an at-risk child. The most widely
used treatments for pediatric osteoporosis, intravenous bisphosphonates, are currently recommended first-line for the treatment of pGIO. It is recognized, however, that even early identification of bone fragility, combined with timely introduction of the most potent bisphosphonate therapies, may not completely prevent osteoporosis progression in all contexts. Therefore, prevention of first-ever fractures in the highest-risk settings is on the horizon, where there is also a need to move beyond anti-resorptives to the study of anabolic agents.

Introduction
Glucorticoid-induced osteoporosis (GIO) is a potentially debilitating complication of GC therapy in children with myriad underlying disorders that span inflammatory conditions, neuromuscular diseases, malignancies, major organ dysfunction and organ transplantation. Importantly, the underlying conditions themselves often pose significant threats to bone strength that are amplified by supra-physiologic GC therapy. In such cases, whether the child develops osteoporosis teeters on the balance between the effective treatment of the underlying disease and the osteotoxicity of the very therapy used to treat the condition. In some cases, such as pediatric leukemia, effective treatment of the underlying disease with (intermittent) GC therapy usually wins the war. In others, the osteotoxicity of GC therapy may limit the benefits of disease-targeted treatment; for example, GC-associated fractures causing premature loss of ambulation in Duchenne muscular dystrophy (DMD).

To better understand the natural history of osteoporotic fractures and risk factors in the pGIO setting, the Canadian STeroid-induced Osteoporosis in the Pediatric Population ("STOPP") Consortium carried out a six-year, multi-centre observational cohort study in over 500 GC-treated
children with various underlying conditions (1-7). Among the most informative observations arising from the STOPP study were that vertebral fractures are a clinical signature of pGIO, they align with the period of maximal GC exposure (and thereby usually occur early in the GC treatment course), and they are frequently asymptomatic (thereby going undetected in the absence of routine spine imaging). The STOPP Consortium also unveiled that even asymptomatic vertebral fractures are associated with an increased risk of future vertebral fractures and, when left untreated, may progress to more advanced collapse in those with persistent risk factors. These observations led to a paradigm shift in the monitoring and diagnosis of GC-treated children, one that placed vertebral fracture identification at the fulcrum of the pGIO assessment. At the same time, children have the growth-mediated ability to restore normal vertebral body dimensions following vertebral fractures, an important index of recovery that may preclude the need for osteoporosis therapy (8).

To bring these key concepts to life, we discuss three GC-treated children with underlying diseases that themselves can adversely affect bone strength. In so doing, we highlight the spectacular potential for growth-mediated vertebral body reshaping following vertebral fractures, both with and without bisphosphonate therapy. We also showcase the attenuated response to IV bisphosphonate therapy in a patient with an aggressive, prolonged GC regimen and progressive disease-related risk factors for bone fragility. These cases provide insight into the day-to-day evaluations and decision-making undertaken by the practitioner and underscore the unmet needs which drive future research in pGIO.
Illustrative Cases

Patient 1: 17-month-old girl with systemic juvenile idiopathic arthritis

A 17-month-old girl with systemic juvenile idiopathic arthritis (sJIA) presented to the Pediatric Bone Health-Osteology Clinic for a routine skeletal health assessment following a nine-month history of GC therapy. She was diagnosed with sJIA at 7 months of age following fever, decreased appetite, lethargy, rash, and swelling of the hands, wrists, and feet. At seven months of age, she was started on prednisone 1 mg/kg/day (79 mg/m²/day in hydrocortisone equivalents [HCE]), with the peak dose reached at 10 months of age (prednisone 2 mg/kg/day, 166 mg/m²/day in HCE). She was also treated with indomethacin and methotrexate soon after diagnosis. At the time of her bone health assessment, there was no history of fractures or unexplained irritability to suggest bone pain, her motor milestones were on target, and she did not have any functional limitations. Her dietary intake of calcium was adequate for age, and she was adherent to vitamin D₃ 400 IU/day. At 13 months of age, she started a progressive prednisone wean that was enabled by the prescription of a biological agent (Anakinra, an interleukin-1 receptor antagonist) at 12 months of age, with continuation of the methotrexate.

On physical examination, she had a Cushingoid facies and dorsal fat pad. Her growth chart was consistent with chronic GC exposure, including linear growth deceleration and excess weight-for-height (Figure 1a). She had mild hyperkyphosis, absence of joint swelling or rash, lack of long bone deformity, and a normal gait. Biochemical parameters of bone and mineral ion metabolism were normal, including an adequate 25-hydroxyvitamin (25OHD) concentration (defined as > 50
nmol/L or 20 ng/dL). At a chronological age (CA) of 16 months, her phalangeal bone age (BA) was 12 months and carpal BA 9 months, according to the Atlas of Greulich and Pyle (9). Her lumbar spine areal bone mineral density (LS aBMD) Z-score was +0.2, which was within the "normal range" and robust for her height Z-score of -3.6 (Figure 1b). A routine lateral spine radiograph showed Genant Grade 2 (moderate) vertebral fractures at T12 and L1 (Spinal Deformity Index [SDI] = 4, Figure 1c), with an exaggerated thoracolumbar kyphosis and loss of lumbar lordosis. Her asymptomatic vertebral fractures underscored the importance of vertebral fracture phenotyping in at-risk children, including the precedence that lateral spine imaging takes over BMD by DXA (since the LS BMD Z-score was not low). This is particularly true for very young infants and toddlers, where the skill needed to acquire adequate DXA images may not always be available in a given institution. Given her young age, planned GC wean, and early signs of linear growth recovery from GC excess (Figure 1a), the decision was made to monitor her skeletal health trajectory optimistically instead of initiating bone protection therapy.

By 2.1 years of age, GC therapy was discontinued; sJIA-targeted therapy was also subsequently discontinued (at 3.5 years of age). During follow-up visits, she showed marked improvement in her height velocity (Figure 1a), early signs of vertebral body reshaping but with superior endplate depression at T12 and L1 (Figure 1b), and a persistently normal LS aBMD Z-score trajectory (Figure 1c). At 5 years of age, there was ongoing normalization of T12 and L1 vertebral heights in the absence of bone protection (bisphosphonate) therapy, but persistent irregularity and depression of the T12 and L1 superior endplates. This finding was consistent with residual fracture healing plus intervertebral disc herniation (similar to the appearance of Schmorl's nodes) (Figure 1b). At 10 years of age, she remained in clinical remission, continued off sJIA-targeted therapy,
demonstrated a normal LS aBMD Z-score for height (+0.2, height Z-score +0.4) plus near-complete vertebral body reshaping at T12 and L1 (although persistent Schmorl's nodes-appearing superior endplate changes at these levels). She also reported engaging in age-appropriate physical activities without limitations or back pain.

**Patient 2: 5-year-old girl with juvenile dermatomyositis**

A 5-year-old girl presented for evaluation in the Pediatric Bone Health-Osteology Clinic following a diagnosis of juvenile dermatomyositis (JDM) plus the initiation of high-dose GC therapy six months earlier (prednisone 2 mg/kg/day, 202 mg/m²/day in HCE). At the time of referral, she was also receiving intravenous immunoglobulin, methotrexate, and had started a GC wean following favorable clinical evolution on combinatorial therapy. At the time of the bone health assessment, she was on prednisone 0.6 mg/kg/day (75 mg/m²/day in HCE) and reported minimal, mid-thoracic back pain not interfering with day-to-day activities, absence of non-vertebral fractures, and normal mobility.

On physical examination, she appeared Cushingoid, with linear growth arrest noted since GC initiation ([Figure 2a](#)). Her laboratory evaluation showed an adequate 25OHD concentration on vitamin D₃ 400 IU daily. Her spine was straight and there was no pain on palpation over the posterior spinous process. A lateral spine radiograph demonstrated Genant Grade 1 (mild) anterior wedging of T6 and T7 vertebral bodies (SDI = 2, x-ray not available), and her LS aBMD Z-score was -2.4 (low for her height Z-score of +0.4, [Figure 2c](#)). A decision was made not to initiate bone protection therapy at that time, given her potential for recovery that included young age (pre-
pubertal), the GC weaning process, and only mild vertebral collapse with minimal back pain that
did not interfere with quality of life.

At her follow-up visits, she continued to demonstrate increases in height velocity and in LS aBMD
Z-scores consistent with GC weaning; GC therapy was then discontinued at 6.5 years of age. At
8.1 years of age, she experienced a JDM relapse and restarted supra-physiologic GC therapy
(prednisone 0.5 mg/kg/day, 60 mg/m²/day in HCE) along with cyclosporine. A repeat lateral spine
x-ray showed failure of reshaping of the previous anterior wedge fractures at T6 and T7 (x-ray not
available) plus a new vertebral fracture at L1 (Genant Grade 2; total spine SDI = 4, Figure 2b). A
trans-iliac bone biopsy (a technique restricted to highly specialized centres) was most notable for
a profoundly reduced formation rate/bone surface at 19% of the healthy average, Figure 2d, left
panel). Given the progressive vertebral collapse and re-initiation of GC therapy, she was started
on intravenous (IV) pamidronate at the age of 9.5 years (Figure 2b). Her multi-site aBMD Z-score
parameters pre-pamidronate were low for her height Z-scores: LS -0.7, Total Hip -0.7, and total
body less head (TBLH) -1.5; height Z-score +0.6. (Figure 2c).

After three years of IV pamidronate, she showed improvement in her vertebral dimensions (Figure
2b), increases in LS, Total Hip, and TBLH aBMD Z-scores (Figure 2c), complete resolution of
her back pain, and normal height velocity (Figure 2a). At that time, her JDM was well-controlled
on mycophenolate mofetil and plaquenil; therefore, her GC therapy was weaned to discontinuation
at the age of 12 years, followed by discontinuation of pamidronate at the age of 12.7 years. In the
years after GC and pamidronate discontinuation, she achieved further reshaping of vertebral bodies
(Figure 2b), ongoing increases in her multi-site aBMD Z-score parameters (LS BMD Z-score +1.3
[Δ +2.0 compared to pre-pamidronate], Total Hip +0.9 [Δ +1.6] and TBLH +0.3 [Δ +1.8]; height Z-score at the time was +0.9 (Figure 2c). In addition, she demonstrated an increase in her transiliac cortical thickness and trabecular number (Figure 2d, right panel). She was followed until 18 years of age; during this time, she required occasional, short bursts of supra-physiologic pulse GC therapy for flare-ups and underwent menarche at 12.5 years of age. At last follow-up, she had complete restoration of normal vertebral dimensions following GC and pamidronate discontinuation (first evident at 15 years of age, SDI =0, Figure 2b) and an appropriate LS aBMD Z-score for age, sex and height (Figure 2c, height Z-score +1.2).

Patient 3: 6.9-year-old boy with Duchenne muscular dystrophy

A 6.9-year-old boy was seen in the Pediatric Bone Health-Osteology Clinic for a routine skeletal health assessment in the context of GC-treated DMD. On history, he was diagnosed with DMD (deletion of DMD exons 48 to 51) at the age of 3.5 years. He was started on deflazacort 0.9 mg/kg/day (60 mg/m²/day in HC equivalents) (10) at 5.9 years of age. At first assessment, he had no back pain nor history of fractures. He was mobile, including climbing the stairs, although slower relative to peers. He was on vitamin D₃ 800 IU daily and had been for two years. On examination, his height Z-score was -1.1 and weight Z-score -0.5. There was no evidence of Cushingoid features, his spine was straight and there was no pain on palpation over the posterior spinous process. His multi-site aBMD Z-scores by DXA showed the following: LS -1.8, Total Hip -1.8, and TBLH -2.1 (all low for height). His lateral spine x-ray showed no evidence of vertebral fractures.
At his one-year follow-up visit (8 years of age), he had an intermittent history of back pain but a lack of non-vertebral fractures. He did not develop significant weight gain on deflazacort, but he did have a decline in his linear height velocity (Figure 3a) with mild Cushingoid features. There was mild tenderness on palpation over the posterior spinous processes in the mid-thoracic region, and he was pre-pubertal. Serum c-telopeptide of type I collagen (CTX) and bone-specific alkaline phosphatase (BS-ALP) were below average at this time (Z-scores for both -1.5) and remained low thereafter. He had significant BA delay for a CA of 9 years, though phalanges were less delayed (six to seven years) than carpals (5 years). Biochemical parameters of bone and mineral ion metabolism were unremarkable, including a serum 25OHD concentration. Lateral spine x-ray showed mild anterior wedging at T11 that did not quite meet fracture criteria but that was also not consistent with anterior physiological rounding (SDI = 0) (Figure 3b) and LS aBMD Z-score declined to -2.3 (Δ -0.5 from baseline at 6.7 years of age, Figure 3d). Given minimal changes at T11 on his lateral spine x-ray (accompanied by declines in LS aBMD Z-scores) in the context of persistent risk factors and a disease setting known to be at high risk for fragility fractures, he was started on IV zoledronic acid (IV ZA) at 8.5 years of age (annual dose 0.1 mg/kg/year divided six monthly), following a trans-iliac bone biopsy (Figure 3e).

His back pain resolved completely post-ZA. In view of his linear growth delay, he underwent endocrine testing that revealed normal thyroid function and Insulin-Like Growth Factor-1 (IGF-1) concentrations; however, he failed a clonidine and arginine growth hormone stimulation test (peak growth hormone 2.2 ug/L at the age of 10.3 years, N: >10). He started recombinant human growth hormone (rhGH) at 13 years of age (0.03 mg/kg/dose, six days per week); this was tolerated uneventfully but ultimately discontinued at the patient's request after 1.5 years due to lack of
significant improvement in height velocity despite prescription adherence (Figure 3a). He had spontaneous puberty at the age of 13 years and complete loss of ambulation at 14.9 years.

At 10.8 years of age, his IV ZA dose was decreased from 0.1 mg/kg/year to 0.05 mg/kg/year, given his stable vertebral fracture status and normal LS aBMD Z-score; he remained on this dose throughout his pediatric years. At his last visit (17.8 years of age), he continued to receive IV ZA therapy, with marked improvement in his LS aBMD Z-score (-0.3 at the most recent visit; Δ+2.0 compared to pre-treatment), whereas his Total Hip aBMD Z-score progressively declined (-3.5 at most recent visit; Δ-0.8). His TBLH aBMD Z-score was stable, and his height Z-score remained low at -4.4 (Figures 3a and d). Despite significant improvements in LS aBMD Z-scores on IV ZA throughout childhood (Figure 3d, also evident on lateral spine x-ray as densification of the vertebral endplates), his x-ray showed mild, progressive vertebral height loss, particularly in the lumbar region (all asymptomatic, Figures 3b and c). Figure 3e shows the patient's response to bisphosphonate therapy on trans-iliac bone biopsy. Unlike in Patient 2 (Figure 2d), the dystrophinopathy plus GC-induced growth impairment in Patient 3 prevented the typical growth-mediated increase in cortical thickness and trabecular number on potent anti-resorptive therapy. Nevertheless, it was anticipated that the degree of osteoporosis on trans-iliac bone biopsy would have been more severe in the absence of treatment. At the time of discharge to adult care at 17.8 years of age, his BA was close to 16 years at the phalanges and 12.5 years at the carpals. Therefore, he was recommended to continue pediatric IV ZA dosing (0.05 mg/kg divided every six months; maximum dose 4 mg) and to transition to annual adult dosing once epiphyses had fused (4 mg per dose). Upon transition, his pediatric-to-adult transition physicians discussed that he would
continue bone protection for as long as he was on GC therapy or longer if there was back pain or new fractures (provided the benefit: risk profile for doing so remained favourable).

Background

Most of the underlying diseases for which GC are prescribed carry an increased risk of skeletal fragility, particularly inflammatory disorders and hematological malignancies because of the adverse effect of disease-related cytokines on skeletal metabolism (e.g. interleukin 6 and 1, tumour-necrosis factor-alpha) (11) and neuromuscular disorders such as DMD. Even beyond the skeletal off-loading of DMD, the aberrant muscle-bone interactions in this condition that involve muscle-derived myokines, bone-derived osteokines, and shared cytokines catalyze common signalling pathways to incite muscle fibrosis, inflammation and bone loss (12).

In addition to disease-related factors, GC have both direct, and indirect, adverse effects on the growth plate and developing skeleton, as recently reviewed in detail (13,14), and outlined in Figures 4a. As shown in Figure 4b, GC wreak havoc on the mechanostat model of bone strength development by interfering at virtually every stage of the cascade (13,15,16); therefore, it is not surprising that GCs are potent disruptors of bone strength.

To unravel the myriad GC effects on the developing skeleton from a practical perspective, natural history studies have taught us to categorize GC-treated children into three over-arching groups (Figure 5): those with aggressive but more limited GC exposure (e.g. children with leukemia), those with variable GC exposure (e.g. children with GC-treated inflammatory disorders and
nephrotic syndrome), and those with aggressive and long-term (even permanent) GC exposure (e.g. GC-treated DMD). This categorization tunes the practitioner to a pivotal consideration that distinguishes pediatric from adult GIO management in a fundamental way: whether a child is likely to fully recover from GC-induced osteotoxicity in the absence of bone-targeted therapy (including reclamation of normal vertebral dimensions following vertebral fractures). The "potential for medication-unassisted recovery from GIO" is indeed central to the overall approach in children, as discussed in the ensuing sections.

Monitoring and Diagnosis

One of the most important lessons arising from the STOPP study was that vertebral fractures are more frequent in children with GC-treated children than non-vertebral fractures, underscoring the vulnerability of the trabeculae-rich spine to the adverse effects of GC. Pediatric vertebral fractures are extremely rare in the absence of trauma (17), but studies have shown in the six years following GC initiation that vertebral fractures occurred in one-third of children with leukemia and 16% of children with rheumatic conditions (4,7) and up to 75% of boys with GC-treated DMD (18). By demonstrating that vertebral fractures defined according to the modified Genant semi-quantitative method (19,20) associated with clinically relevant variables including LS aBMD Z-scores, back pain, second metacarpal percent cortical area, and an increased risk of future fractures (1,4,6,21), the STOPP Consortium validated that > 20% loss in vertebral height ratio is an acceptable definition of a vertebral fracture in children.
The most compelling observation that validated the use of the Genant semi-quantitative method in children arose from the longitudinal study of children with leukemia, where Genant-defined vertebral fractures at diagnosis were a strong predictor of new vertebral and long bone fractures over the ensuing five years (4). Lateral spine imaging by conventional radiography or DXA-based vertebral fracture assessment (VFA) (22) should be evaluated by a health care professional with trained expertise, including the ability to distinguish vertebral fractures from normal pediatric variants (23). Figure 6a benchmarks images in this review to a normal spine radiograph in a GC-treated child, and Figure 6b provides an example of normal anterior physiological rounding in the mid-thoracic region; such anterior rounding is characteristic of the immature spine and must not be mistaken for a Grade 1 fracture. Figures 7a, b, c, d and e show signs of vertebral fractures according to the Genant semi-quantitative method; in equivocal cases, qualitative signs of vertebral fractures may aid the clinician in the diagnosis (endplate interruption, anterior cortical buckling, and loss of endplate parallelism). Genant-defined severity grades correspond to the degree of vertebral height ratio loss, as follows: Grade 1 (mild) > 20 to ≤ 25%, Grade 2 (moderate) > 25% to ≤ 40%, and Grade 3 (severe) > 40% (19,20).

Endplate interruption and anterior cortical buckling are usually associated with a more than 20% reduction in vertebral height ratio. Loss of endplate parallelism can be apparent in vertebral bodies which fall short of reaching fracture grade but are nevertheless on the pathway to fracture, and with anterior physiological rounding. Once a vertebral body reaches fracture grade, loss of endplate parallelism is almost universal (the exception being symmetrical crush fractures). Symmetrical crush fractures are at greatest risk of going undetected because they retain a relatively normal overall vertebral shape; this is especially true when there are multiple adjacent crush...
fractures. Such fractures are assessed by semi-quantitative comparison of the posterior height of
the vertebral body in question to the posterior height of the vertebral body above (to determine if
there is > 20% loss in height ratio); widening of the intervertebral spaces may also provide visual
clues to the diagnosis of symmetrical crush fractures.

Even a single, low-trauma long bone fracture can be a major osteoporotic event in children with
GC-treated disorders. Although forearm fractures are extremely common in childhood, the clinical
context surrounding the fracture (low or high trauma), plus the GC-treated child's clinical profile
(height, body mass index, puberty, BMD trajectories, GC dose, and duration, presence or absence
of VF, Cushingoid appearance, and disease activity) usually provides sufficient information to aid
the physician in assessing the fracture's clinical significance. Comminuted fractures, and those
with atypical displacement, are also significant, especially in the absence of trauma. Lower
extremity fractures are particularly concerning in GC-treated DMD due to their association with
permanent, premature loss of ambulation (8), along with unexpected mortality due to fat embolism
syndrome (24).

One of the questions with which clinicians often struggle is when to initiate bone health monitoring
in a GC-treated, or previously GC-treated, child. Vertebral fractures have been diagnosed as early
as four to six months following GC initiation in children with GC-treated inflammatory disorders
and DMD (21,25). With this in mind, bone health monitoring, including lateral thoracolumbar
spine imaging, should start around the time of GC initiation in long-term, high-dose GC-exposed
populations such as DMD (26), and as soon as possible in other diseases where children are
anticipated to receive ≥ 3 months of daily oral or IV GC therapy. The rationale for this guidance
is that none of the natural history studies to date in GC-treated children have reported new (incident) vertebral fractures earlier than four months following GC initiation (when a baseline spine x-ray has been available to discern incident fractures) (21). Furthermore, longitudinal natural history studies have shown that the peak vertebral fracture incidence in childhood leukemia (4) and rheumatic conditions (7) occurs at 12 months following GC initiation, which corresponds with the timing of maximal annual GC exposure. As such, the first year of GC therapy is a critical time to monitor for early signs of bone fragility, based on the premise that this is also likely to be a period of substantial GC exposure.

Figure 8a shows the main factors in deciding whether to initiate bone health monitoring beyond the GC exposure criteria, including back pain, a history of even a single, low-trauma long bone or vertebral fracture, poorly controlled underlying disease, or chronic sub-normal mobility (all in the serious acute or chronic illness settings). Figure 8b summarizes the 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 (26,27). The heart of the bone health monitoring paradigm is lateral spine imaging at baseline and annually for as long as the patient is GC-treated (and potentially longer if there is ongoing, poorly controlled disease, back pain or sub-normal mobility). Baseline and annual BMD parameters (particularly lumbar spine and, if the patient is capable, total hip or lateral distal femur BMD) are also suggested given the potential for differential effects of GC therapy and sub-normal mobility on the spine versus extremities. Total body (less head) DXA is useful in understanding the GC-treated child’s changes in body composition (fat and lean mass). Back pain, increases in BMI Z-scores, decreases in LS aBMD Z-scores, bone age delay, decreases in height velocity, worsening disease activity and/or Cushingoid features may prompt
consideration for an earlier BMD than annually; a drop in LS aBMD Z-score over two consecutive measures by $\geq 0.5$ or back pain should also prompt consideration of lateral spine imaging sooner than annually, in order to detect vertebral fractures as close to their first emergence as possible (26).

Over the last decade or so, the pGIO field has moved away from a BMD-centric towards a fracture-focused approach to the diagnosis, for numerous reasons. First and foremost, fractures are the most clinically relevant endpoint, with BMD a surrogate for bone strength. Secondly, BMD can be low due to size artefact (i.e. short stature), and Z-scores can decline due to poor linear height velocity, weight loss, or delayed puberty. Furthermore, BMD Z-scores can be greater than -2.0 in GC-treated children with fractures (1,21,25), a fact which invalidates the use of a specific threshold to trigger care pathways in the management of pGIO. In addition, BMD Z-scores can vary up to 2.0 standard deviations depending on the normative data that is used to generate the Z-scores (28), further rendering a BMD threshold-based approach that triggers care pathways impractical. BMD interpretation is therefore most challenging when used as a single cross-sectional measurement. However, as the cases highlight, longitudinal BMD trajectories are highly informative as they typically mirror the child’s overall clinical evolution. In routine care, BMD is but one of numerous pieces of information that orients the pediatrician to whether the child’s evolution is in a positive or negative direction, whether the child has had a clinically significant fracture, and how the child is responding to bone-targeted treatment.

Once the diagnosis of osteoporosis has been made, the next step is to determine whether the patient has the potential to undergo spontaneous (i.e. medication-unassisted) recovery from bone fragility.
The juvenile skeleton has tremendous potential to recover from osteoporosis, provided threats to bone health have abated and 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 (8). 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 and lumbar vertebral fractures were at increased risk for persistent vertebral deformity (8). Figure 9a provides an algorithm which walks the clinicians through the steps involved in understanding a child’s potential for medication-unassisted recovery. Figure 9b provides a "quick reference" summary of the main considerations in this pivotal adjudication.

Prevention and Treatment

Prevention of bone fragility in the GC-treated child starts with conservative measures to optimize bone strength including maintenance of a healthy weight, identifying and treating vitamin D and other nutritional deficiencies, monitoring and treating delayed puberty, fall prevention strategies, and optimization of weight-bearing (within the limits of the underlying disease). Delayed puberty is virtually universal in children with daily, GC-treated DMD. Short stature is a frequent complication of supra-physiological GC dosing that often involves "end-organ resistance" to rhGH therapy due to GC-induced growth plate toxicity; low growth hormone (GH secretory status may also be a factor in GC-induced growth delay. Treatment with rhGH is typically entered into on a case-by-case basis after careful review of the child’s residual growth potential, predicted
versus mid-parental height, anticipated GC prescription, GH secretory status, and psychological orientation to the growth delay. Short stature is often profound in GC-treated DMD at standard, supra-physiological daily doses as shown in Patient 3; rhGH is not recommended as standard of care due to insufficient evident about the benefits and risks, but may be considered on a case-by-case basis as outlined above (26).

The decision to treat a child with a bisphosphonate or not determines the nature and frequency of follow-up. For children anticipated to recover from osteoporosis, annual follow-up for 1-2 years to affirm the anticipated, favourable prognosis is a reasonable approach (including BMD studies, lateral spine imaging if vertebral fractures were part of the osteoporotic phenotype, and a 25OHD concentration). For patients with limited potential for spontaneous recovery, treatment with intravenous bisphosphonate therapy is the standard of care, Figure 10). Importantly, a patient's "fitness" for bisphosphonate therapy should be assessed prior to embarking on treatment, including adequate dietary and/or supplemental intake of calcium and vitamin D, euphasphatemia and eucalcemia, 25OHD sufficiency, and adequate renal function. IV ZA is contraindicated in patients with acute renal failure, and dose adjustments to IV therapy are required for patients with estimated glomerular filtration rates less than 60 ml/min/1.73 m². Bisphosphonate-induced hypocalcemia is a well-known phenomenon; however, it is less appreciated that hypophosphatemia is also a frequent consequence post-bisphosphonate therapy, particularly in patients with pGIO and other chronic illnesses (29,30), and may necessitate phosphate supplementation.

The first infusion side effects of IV bisphosphonate therapy can precipitate adrenal insufficiency in patients on chronic GC therapy, even when they are taking daily supra-physiological doses. This
is because the GC duration of action on once-daily doses may not be sufficient to cover the entire 24-hour period leading up to the next GC dose (10,31). Therefore, it is prudent 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 (i.e. fever, vomiting) (32,33). Boys with DMD may experience flu-like symptoms even beyond the first dose and require repeated home management guidelines for steroid stress dosing.

For many years, IV pamidronate was the most frequently used agent in children with osteoporosis following the inaugural, observational study in the late ’90s, which showed improved pain, mobility, and reshaping of vertebral bodies on pamidronate in children with moderate to severe osteogenesis imperfecta (OI) (34). IV ZA has since been introduced, given the advantage that it can be given over a shorter period of time and less frequently (35,36); ZA is 100 times more potent than pamidronate (37). A randomized study comparing the effect of pamidronate and ZA in OI showed that ZA had similar effects on LS BMD Z-scores and fracture rates over 12 months (35).

Of the oral agents, alendronate and risedronate have been the most extensively studied, with reports confirming that the oral bioavailability of alendronate in GC-treated children is < 1%, similar to adults (38,39). Given the low oral bioavailability of oral agents, it is not surprising that side effects are also reduced, though at an apparent cost to treatment efficacy.

Despite the formidable challenges in conducting clinical trials in children with osteoporosis, there are now a number of randomized controlled trials of oral and IV bisphosphonates that have been
carried out in primary (40-46) and secondary (47-53) osteoporosis of childhood. Collectively, nearly all of the controlled IV and oral bisphosphonate therapy trials have shown significant increases in LS BMD Z-scores (both height-adjusted and unadjusted). The two routes of administration more clearly distinguish themselves, however, with respect to vertebral body reshaping (in patients with growth potential) (54). Therefore, it is on these grounds that the response to IV versus oral bisphosphonate therapy is adjudicated.

Based on observational studies, it is expected that fractured vertebral bodies in OI will undergo reshaping with bisphosphonate therapy (36,54-56), thereby providing a key index of benefit. The controlled trials to date in growing children with OI which quantified vertebral body height clearly showed increases in those receiving IV bisphosphonate therapy (45,57,58), whereas none of the controlled oral bisphosphonate studies in OI where it was measured showed a positive effect on vertebral height (40-42,59). In fact, vertebral fracture rates were more frequent in patients with OI on risedronate (40), and bone turnover markers increased on average (instead of the expected decrease) on risedronate in the study of children with rheumatic disorders by Rooney et al. (48).

In a large, randomized trial of daily oral alendronate for moderate and severe pediatric OI (44), there was no effect of alendronate on the cortical width of trans-iliac specimens. In contrast, this is a key structural index derived from a precise measurement with a known positive response in OI to IV bisphosphonate therapy (60). Overall, these data support the use of IV bisphosphonate therapy first-line in childhood osteoporosis; the increases in BMD on oral agents nevertheless suggest that oral may be a reasonable therapy in situations where IV bisphosphonates are unavailable.
One of the most important concepts that we wish to impart is the expertise that is needed to assess longitudinal spine imaging in children to detect vertebral fractures and to adjudicate changes in vertebral body structure over time according to a standardized approach. The SDI (the sum of the Genant Grades, and therefore a metric of overall spine fracture burden that considers both the number and severity of fractures) is particularly useful in the pediatric setting where static, worsening, and improving vertebral deformity influence management decisions.

Here, we provide examples of quantitative and qualitative signs of vertebral fractures in addition to changes in the SDI over time. These changes run the gamut from spontaneous improvement without bisphosphonate therapy in Patient 1 with sJIA, bisphosphonate-assisted vertebral body reshaping while on GC therapy plus ongoing improvement in vertebral dimensions post-GC and post-bisphosphonate discontinuation in Patient 2 with JDM, and progressive vertebral deformity despite a robust LS aBMD Z-score response and early introduction of bisphosphonate therapy in Patient 3 with DMD (an aggressive form of pGIO where linear growth is also invariably affected by the high and prolonged GC exposure, thereby interfering with growth-mediated vertebral body reshaping).
Special Considerations in Children at the Extreme Ends of Potential for Recovery from GIO: Leukemia and Duchenne Muscular Dystrophy

Patients at the extreme ends of the potential for recovery from pGIO merit particular consideration. Children with leukemia represent the prototypical example of the potential for vertebral body reshaping in the vast majority. In the longitudinal STOPP study, 16% of children with leukemia had prevalent vertebral fractures at diagnosis (Figure 11), and 1/3 of children sustained new vertebral fractures in the ensuing six years (most of which occurred in the first 24 months) (4). At the same time, the STOPP Consortium also demonstrated that almost 80% of the children with vertebral fractures underwent complete vertebral body reshaping over six years following diagnosis, while the remainder underwent partial (15%) or absent (5%) reshaping (4). 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. Because of the tremendous drive for recovery from osteoporotic fractures in leukemia, patients with back or bone pain undergo targeted imaging per the usual clinical care response to pain location. Spine imaging and the need for osteoporosis therapy thereafter are dictated by the child’s pain status, BMD Z-score trajectory, potential for recovery from fractures, and functional mobility.

Recent international guidelines recommend carrying out a BMD at the end of leukemia therapy and, if > 1.0 standard deviation for age and sex, to repeat the measurement at age 25. For those with lower values, it was recommended to implement the local standard of care due to a lack of evidence otherwise (61). Questions remain about the treatment approach in those with residual low BMD at the end of growth, given data arising from a pediatric leukemia survivor clinic showing
an increased frequency of non-digit fractures (62). 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 (62,63); this is an important research question going forward.

DMD is at the other end of the spectrum, with the absence of evidence for spontaneous vertebral body reshaping or reclamation of BMD based on current knowledge and experience. Even with early bisphosphonate treatment, bone health deficits persist, including reduced long bone cross-sectional diameter (Figures 12a and b) and progressive vertebral collapse (as shown in Patient 3). Tibia pQCT clearly demonstrates in three dimensions that small bone cross-sectional area is a defining aspect of the skeletal phenotype in DMD. This structural aberrancy is unchanged on bisphosphonate therapy because anti-resorptive treatment does not foster periosteal apposition (a growth- and muscle-strength and mechanical forces-driven process) (Figure 12a). The profound effect of the myopathy is shown in Figure 12b, a four-year-old with a major femur fracture prior to initiation of GC therapy for DMD.

The progressive vertebral collapse despite normal LS BMD Z-scores for age, sex, and height in IV bisphosphonate therapy in Patient 3 is also concerning. Studies have shown that adults with vertebral deformity following vertebral fractures have chronic pain and functional limitations (64); another adult study showed restrictive lung disease in those with versus without vertebral fractures (65). The STOPP Consortium reported reductions in stature among children with leukemia and vertebral fractures (66); whether vertebral fractures are linked in children to restrictive lung disease and excess mortality is unknown. On a positive note, a retrospective study showed that both GC
and bisphosphonate therapy were associated with longevity in DMD (67); whether the favourable
association between bisphosphonate therapy and longevity was due to relative preservation of
vertebral heights, prevention of fat embolism syndrome, or another mechanism remains unclear.
We have recently undertaken studies which suggest the hyperlordosis of ambulatory DMD may
contribute to the relatively higher rate of lumbar fractures in this setting compared to other GC-
treated children (Figures 12c and d) (68); if so, this observation underscores the importance of
effective treatment for the underlying myopathy in order to prevent both vertebral and overall spine
deformity.

Current guidelines advocate for continuing bisphosphonate treatment in patients receiving ongoing
GC therapy who exhibit moderate to high risk of fracture (69,70). In DMD, the permanency and
high-risk nature of osteoporosis risk factors, including progressive myopathy, loss of ambulation,
and high-dose GC therapy, suggest the need for considering long-term bone protection therapy in
this setting. However, there are no studies that have formally assessed the risks and benefits of
continuing bisphosphonate therapy post-epiphyscal fusion among individuals with DMD who
initiated therapy in childhood. Further research in this area is needed, given theoretical concern
about adverse effects arising from chronic bone turnover suppression in an already low bone
turnover state.

Given the tremendous morbidity arising from pGIO in DMD despite the introduction of
bisphosphonate therapy at the earliest signs of fractures, efforts are underway to ignite research
programs targeting osteoporosis therapy prior to first-ever fractures (including strategies that move
beyond mono-therapeutic anti-resorptive therapy in hopes that osteo-anabolic strategies may
positively impact not only BMD but also bone structure). One such agent, teriparatide, was studied in six individuals with DMD (ranging in age from 13.0 to 22.1 years of age), giving rise to modest increases in PINP and stable BMD trajectories over 1-2 years (71). These preliminary data provide proof-of-principle that further study of osteo-anabolic agents is justified in this condition.

Although gene and genetic therapies are now approved in some countries for the treatment of DMD, none of the advanced treatments are robust enough to recommend the removal of GC therapy from the therapeutic regimen (72). This means that GC therapy is here to stay for the foreseeable future in DMD, placing an onus on the pediatric osteology community to work with DMD partners to improve the aggressive pGIO that currently defines DMD.

Researchers have investigated whether intermittent prednisone (10 days on, 10 days off) are bone- and growth-plate protective in boys with DMD. The short answer is yes (fewer prevalent vertebral fractures) (73), but at a cost to muscle strength relative to daily prednisone (73,74). Vamorolone, a novel dissociative steroidal drug, has been developed in an effort to "separate the good from the bad" (75-79). In a recent randomized, placebo- and prednisone-controlled clinical trial (NCT03439670) in boys with DMD, vamorolone showed comparable efficacy for muscle function relative to daily prednisone, plus improved linear height velocity and bone turnover markers (79). Preliminary, post-hoc analyses also suggest vertebral fracture rates may be lower (80); the impact on long bone fractures related to prednisone remains unknown. However, vamorolone also caused dose-dependent adrenal suppression (81), a critical message to convey given the life-threatening nature of this co-morbidity.
Summary and Conclusions

There are a number of diagnostic and management principles that are similar across the lifespan, including the importance of vertebral fractures as a major sign of osteoporosis-related morbidity, and the need for timely identification and treatment of osteoporosis in order to prevent downward health spirals (e.g. femur fractures in boys with DMD and in the elderly leading to permanent loss of ambulation). As such, GIO management should be viewed along a continuum, with the stage set in childhood for optimization of bone strength across the lifespan (82). At the same time, there are uniquely pediatric features that require a different approach to clinical care pathways; these are driven by the potential for dramatic densitometric and structural recovery following resolution of risk factors in the presence of residual growth potential. Overall, current evidence affirms the need for pro-active approaches in childhood to optimize pediatric outcomes and prevent permanent structural damage and BMD deficits later in life.

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Authors' Contributions

Dr. Bakhamis prepared the Case Reports and Figures under the supervision of Drs. Ward and
Koujok. Dr. Koujok read the spine images, and Dr. Ward wrote the manuscript. All authors
carefully reviewed and approved the manuscript prior to submission.

Data Availability

Data sharing is not applicable to this article as no original datasets were generated or analyzed fo
this “approach to the patient” manuscript.
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**Figure Legend:**

**Figure 1a, b, c (Patient 1)** describes osteoporotic vertebral fractures in a young girl with GC-treated systemic juvenile idiopathic arthritis who underwent complete vertebral body reshaping with GC weaning, well-controlled underlying disease, and significant residual growth potential. **Figure 1a** highlights growth deceleration while on GC therapy, and an increase in height velocity during and following her GC wean. The increase in height velocity provided an early sign of her potential to undergo spontaneous (medication-unassisted) vertebral body reshaping, informing the decision to withhold osteoporosis-targeted therapy. **Figure 1b** shows lack of significant impact of GC therapy on the LS aBMD Z-score trajectory. This observation highlights the importance of vertebral fracture identification independent of a given LS aBMD Z-score threshold in the pGIO setting (for further discussion see text). **Figure 1c** demonstrates this patient's reclamation of near-normal vertebral dimensions following Grade 2, GC-induced vertebral fractures at T12 and L1. She also demonstrated intervertebral disc herniation at the superior endplates of the affected vertebrae (similar to the appearance of Schmorl's nodes). Her young age, significant residual
growth potential and resolution of osteoporosis risk factors were the main factors in her improved vertebral body structure.

**Abbreviations:** a = areal, BMD = bone mineral density; GC = glucocorticoid; pGIO = pediatric glucocorticoid-induced osteoporosis; L = lumbar; LS = lumbar spine; MPH = mid-parental height; T = thoracic.

Figure 2a, b, c, d (Patient 2) describes the skeletal health of a girl with GC-treated juvenile dermatomyositis who received two courses of daily, supra-physiological GC therapy for the treatment of her rheumatic condition; the second course was associated with vertebral fractures and an ongoing need for GC treatment, prompting IV bisphosphonate therapy. Figure 2a shows weight loss during the first GC wean, growth deceleration with the second GC course, and attainment of a normal adult height in the years following her GC wean. These observations were consistent with absence of a permanent GC effect on height plus well-controlled underlying disease during the critical growing years. Figure 2b highlights the patient's vertebral fracture trajectory, including vertebral body reshaping plus densification of the vertebral endplates on pamidronate and ongoing vertebral body reshaping post-GC and post-pamidronate discontinuation. The thoracic spine is shown at the top (where available) and lumbar spine at the bottom. Her vertebral fracture evolution on these spine x-rays was as follows: normal L1 vertebral body at 7 years of age (thoracic and lumbar SDI = 0). At 9 years of age, she developed an incident (new) Genant Grade 2 vertebral fracture at L1 (SDI = 2); at 11 and 12 years, she demonstrated L1 partial reshaping (SDI = 1) followed by complete vertebral body re-shaping at 15 years of age (SDI = 0). Figure 2c describes the patient's multi-site BMD parameters by DXA, highlighting the supra-physiological aBMD Z-score trajectories at all three sites (LS, total hip and TBLH) on IV
pamidronate, while also receiving GC therapy. The uniform decline in BMD parameters post-pamidronate cessation was expected (with values remaining well within the normal range), as the patient returned to her normal "endogenous" BMD set-point following bisphosphonate discontinuation. Figure 2d shows the patient's trans-iliac bone sample taken for bone histomorphometry pre- and two years post-pamidronate, highlighting the main effects of IV bisphosphonate therapy on bone tissue in children – increases in cortical width and in trabecular number (both growth-mediated). This outcome is caused by the anti-resorptive effect of bisphosphonate therapy on the endocortical surface combined with the uncoupled, innate periosteal apposition that occurs during growth on the periosteal surface. The observed bone tissue effects on IV pamidronate underscore the importance of treating osteoporosis during the growing years, a period that is exquisitely sensitive to the bone density- and structure-enhancing effects of bisphosphonate therapy.

**Abbreviations:**
a = areal; BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; GC = glucocorticoid (s); IV = intravenous; JDM = juvenile dermatomyositis; L = lumbar; LS = lumbar spine; MPH = mid-parental height; SDI = Spinal Deformity Index; TBLH = total body less head.

Figure 3a, b, c, d, e (Patient 3) highlights the skeletal health trajectory of a boy with DMD who started daily, supra-physiological GC therapy at 5.9 years of age and IV pamidronate at 8 years for early signs of vertebral collapse. In contrast to Patients 1 and 2, this patient had persistent and permanent threats to bone health, including long-term GC therapy plus a progressive myopathy. These "disease context" features have led to guidelines that support initiating bone protection therapy at early, rather than late, signs of bone fragility. Figure 3a describes the profound growth
arrest of GC-treated DMD, including lack of response to rhGH. The slight improvement in linear growth after 14 years of age was attributed to progression through endogenous puberty. Spontaneous puberty in the daily GC-treated DMD setting is unusual; the need for pubertal induction is more typical in this setting. Figures 3b and c highlight the patient's vertebral fracture trajectories. Figure 3b (thoracic spine) demonstrates minimal anterior wedging at T11 that did not quite meet fracture criteria at 8 and 11 years of age (defined as > 20% loss of vertebral height ratio); however, given the natural history of progressive vertebral collapse in the GC-treated DMD setting combined with a significant decline in total hip aBMD Z-score, bone protection therapy (IV ZA) was initiated at 8 years of age. At 12 years of age, he demonstrated an incident (new) Genant Grade 1 vertebral fracture at T7. At 14, 16 and 17 years of age, the Grade 1 vertebral fracture at T7 was stable, with evidence for a global decrease in height at T8 that did not quite meet fracture criteria. Figure 3c (lumbar spine) shows normal lumbar vertebrae at 8 and 11 years of age, followed by a mild decrease in height at L3 (at 12 years of age) that did not meet the fracture criteria. At 16 years of age, there was a new Genant Grade 2 vertebral fracture at L5 with buckling of the anterior cortex at the superior endplate (red arrow) and a new Genant Grade 1 vertebral fracture at L4. There was also a Grade 1 monoconcave fracture at L2 with loss of endplate parallelism. At 17 years of age, his spine x-ray was stable relative to the previous. At 17 years of age, his vertebral deformities remained stable (while continuing IV bisphosphonate therapy as he transitioned to adult care). Figure 3d demonstrates the multi-site aBMD Z-score trajectories on IV ZA therapy, showing favourable evolution at the spine, progressive decline despite bisphosphonate therapy at the hip, and stabilization for the TBLH measurement. Figure 3e shows the bone structure on trans-iliac bone biopsy in GC-treated DMD treated with IV bisphosphonate therapy. Unlike in Patient 2 (Figure 2d), the dystrophinopathy plus GC-induced growth
impairment in **Patient 3** prevented the typical growth-mediated increase in cortical thickness and trabecular number on potent anti-resorptive therapy. Nevertheless, it was anticipated that the degree of osteoporosis on trans-iliac bone biopsy would have been more severe in the absence of treatment.

**Abbreviations:** $a = \text{areal; BMD = bone mineral density; DMD = Duchenne muscular dystrophy;}$

$GC = \text{glucocorticoid; GH = growth hormone; IV = intravenous; rhGH = recombinant human growth hormone; L = lumbar; MPH = mid-parental height; SDI = Spinal Deformity Index; T = thoracic; TBLH = total body less head; ZA = zoledronic acid.}$

**Figures 4a** outlines the deleterious effect of GC therapy on bone and growth plate metabolism in childhood. **Figure 4b** demonstrates the most important functional consequences of GC-induced bone and growth plate toxicity.

**Abbreviations:** GC = glucocorticoid; OPG = osteoprotegerin; RANKL = Receptor activator of nuclear factor kappa-B ligand.

**Figure 5** provides an overall, thematic approach when considering the management of skeletal health in GC-treated children. The approach to GIO management in children is intimately linked to the known fracture risk in various disease contexts and whether risk factors are transient, variable or persistent. These profiles, in turn, determine whether a child is able to recover spontaneously from bone health threats (without osteoporosis therapy), or require bone protection (i.e. bisphosphonate) therapy.

**Abbreviations:** DMD = Duchenne muscular dystrophy; GC = glucocorticoid; GIO = glucocorticoid-induced osteoporosis.
Figures 6a, b highlight examples of normal spine x-rays in children, including "anterior physiological rounding" in the mid-thoracic region (red stars, Figure 6b). Physiological wedging is apparent in younger children due to lack of, or emerging, ossification of the ring apophyses. This "normal anterior physiological rounding" is distinguished from vertebral fractures in two ways. First, the anterior: posterior height ratio will not meet fracture grade (i.e. will not reach > 20% loss in anterior: posterior height ratio). In addition, there is a slight "posterior bulge" of the vertebral body in physiological rounding. The white arrows show early signs of ring apophysis ossification in this child; once ossification of the ring apophyses is complete, the vertebral bodies take on the more classic "square-like" shape of the mature spine.

Abbreviation: DMD = Duchenne muscular dystrophy.

Figure 7a, b, c, d, and e show examples of vertebral fractures in children with severity grading according to the Genant semi-quantitative method (see text). These include anterior wedge fractures (the most common deformity (a), mono- and bi-concave fractures (b and c), and crush fractures (d). L5 has a unique posterior wedge shape that is not part of the formal Genant semi-quantitative assessment, but can nevertheless undergo fracture (e), particularly in patients with hyperlordosis as in DMD. In addition, qualitative signs of vertebral fractures may be evident, including loss of endplate parallelism (shown throughout these images, a phenomenon which occurs when there is asymmetrical vertebral height loss within and relative to adjacent vertebral bodies), as well as anterior cortical buckling and endplate interruption.

Abbreviations: DMD = Duchenne muscular dystrophy; VF = vertebral fracture; L = Lumbar; T = thoracic.
Figure 8a provides guidance on the criteria for initiating a bone health evaluation in a GC-treated (or previously GC-treated) child. While daily oral or IV GC therapy for ≥ 3 or more months at supra-physiological doses is a defining trigger for a bone health evaluation, the presence of back pain, poorly controlled underlying disease or sub-normal mobility are also important considerations in the need for bone health monitoring (irrespective of GC dose, duration or recency of treatment). Figure 8b outlines the overall approach to monitoring and diagnosis of osteoporosis after a decision to monitor an at-risk child has been made. Note that spine imaging (by x-ray or DXA-based "vertebral fracture assessment") is the fulcrum of the osteoporosis monitoring paradigm in children, given observations that DXA-based BMD Z-scores can be normal in children with overt bone fragility, that BMD Z-scores vary widely depending on the normative data used to generate the Z-scores, and that vertebral fractures (frequently asymptomatic, requiring a pro-active approach to their detection in high-risk settings) are a signature manifestation of pGIO.

Abbreviations: 1,25(OH)₂D₃ = 1,25-Dihydroxvitamin D₃; BMD = bone mineral density; BMI = bone mass index; DXA = dual-energy x-ray absorptiometry; GC = glucocorticoid; IV = intravenous; LS = lumbar spine; pGIO = pediatric glucocorticoid-induced osteoporosis.

Figures 9a, b provide guidance on the initial approach once bone fragility has been identified. The first step, Figure 9a, is to gauge the child's ability to undergo spontaneous recovery from bone fragility (including vertebral body reshaping and reclamation of a normal BMD for age/bone age, height and sex, thereby obviating the need for bone protection therapy). Figure 9b provides a summary of the main factors to consider in the decision to treat with osteoporosis therapy.
Abbreviations: BMD = bone mineral density; DMD = Duchenne muscular dystrophy; DXA = dual-energy x-ray absorptiometry; GC = glucocorticoid; IV = intravenous; VFA = vertebral fracture assessment.

Figure 10 outlines the approach to treatment of pGIO with bisphosphonate therapy once the decision has been made that bone protection therapy is necessary due to lack of potential for medication-unassisted recovery.

Abbreviations: BMD = bone mineral density; GC = glucocorticoid; pGIO = pediatric glucocorticoid-induced osteoporosis.

Figure 11 shows a lateral spine x-ray in a child with painful vertebral fractures due to leukemia, a known manifestation of hematological malignancy that is the diagnosis to rule out urgently. Interestingly, this patient also had a loss of function variant in the LRP5 gene, which may have exacerbated his risk for low BMD and vertebral fractures. In addition, his CBC was not typical for leukemia at diagnosis (lack of hyper-leukocytosis or suppressed marrow activity otherwise), raising the importance of painful vertebral fractures as a hallmark sign of leukemia. Longitudinal studies have shown that nearly 80% of children with vertebral fractures during leukemia therapy will undergo complete vertebral body reshaping without bisphosphonate therapy, with fracture severity (degree of vertebral height loss), fractures in the lumbar region, and residual growth potential negatively influencing the potential for reclamation of normal vertebral dimensions.

Abbreviations: BMD = bone mineral density; CBC = complete blood count; LRP5 = Low-density lipoprotein receptor-related protein 5.
Figures 12a, b, c, d highlight special considerations in the forward-looking management of pediatric GC-treated DMD, the most aggressive osteoporosis of childhood with the least potential for recovery. Figure 12a shows images by tibia pQCT at the 3% (top row), 38% (middle row) and 66% (bottom row) sites. There is a low trabecular vBMD Z-score at the 3% site pre-bisphosphonate therapy (-2.2), with improvement post-therapy (+0.2). At the 38% site, there is low periosteal circumference (-1.3) which drops further despite bisphosphonate therapy (-1.6), as expected. The "gracile" (thin) nature of long bones in DMD is a major risk factor for fractures despite potent antiresorptive therapy, since anti-resorptives do not increase bone cross-sectional diameter. Gracile long bones are a well-known feature of osteoporosis due to neuromuscular disorders, a phenomenon that is exacerbated by the growth-attenuating effects of GC therapy. At the 66% site, where muscle is maximal, an increase in muscle-cross-sectional diameter due to fibrosis is evident in the patient with DMD compared to the control. Figure 12b shows the consequences of long bone structural abnormalities and low BMD in pediatric DMD: a major, low trauma femur fracture prior to GC initiation in a 4-year-old boy. Figure 12c highlights hyperlordosis (unique to the ambulatory phase of DMD, as loss of ambulation typically results in flattening of the lumbar spine due to hip contractures from prolonged sitting). Figure 12d shows the DMD "spinunculus" according to age of the patients, which correlates with the stage of the disease. "Spinunculus", a novel term developed by Dr. Ward's research group, is used to describe the mapping of vertebral fracture frequencies along the length of the spine in a given condition. Note that Figures 12c, d suggest there may be a relationship between spine deformity and the distribution of vertebral fractures in DMD (where a preponderance of lumbar fractures has been observed relative to other GC-treated populations). Together, the observations in Figure 12 harken the need for a bone protection approach that starts as early as possible in the DMD setting, with an agent capable of
not only improving BMD and cortical thickness, but also bone cross-sectional diameter (the latter, which anti-resorptive therapy does not achieve). Effective treatment of the underlying disease with an approach that maximizes muscle strength and minimizes orthopedic spine deformity and fractures as far as possible remain the ultimate goals in this ultra high-risk setting.

**Abbreviations:** BMD = bone mineral density; DMD = Duchenne muscular dystrophy; GC = glucocorticoid (s); IV = intravenous; pQCT = peripheral quantitative computed tomography; v = vertebral.
Figure 1
210x182 mm (DPI)
Figure 2
211x231 mm (DPI)
Figure 3
212x247 mm (DPI)
The Osteotoxicity of Glucocorticoid Excess

- Renal Calcium and Phosphate Reabsorption
- Intestinal Calcium Absorption
- Vitamin D Catabolism
- Chondrocyte Growth Plate Activity
- Osteoclast Bone Resorption
- Apoptosis
- OPG RANKL
- Growth factors
  - Sex steroids
  - Wnt signalling
  - Apoptosis
- Osteoblast Bone Formation

The Impact of Chronic Illnesses on the Mechanostat Model of Bone Strength Development of Childhood

Mechanical Challenges
- Attenuated linear growth
- Decreased muscle mass (due to sub-normal mobility or delayed puberty)

Bone Strength
- Bone Mass

Tissue Strain
- Setpoint
- Effector Signals

Glucocorticoids:
- Decrease osteocyte-mediated mechanosensing
- Impair bone formation
- Accelerate bone resorption (in the early phases of glucocorticoid exposure)
- Increase 25-hydroxyvitamin D catabolism
- Decrease intestinal calcium and phosphate absorption, and increase renal calcium and phosphate excretion
- Attenuate the normally healthy, estrogen-induced lowering of the mechanostat set-up by causing delayed puberty in girls

Figure 4
200x263 mm (DPI)
Figure 5
214x198 mm (DPI)
Figure 6

207x122 mm (DPI)
Figure 7
214x198 mm (DPI)
Figure 8

207x251 mm (DPI)
a. 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

- 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

**Assess the child’s potential to undergo bisphosphonate-unassisted restitution of BMD and reshaping of fractured vertebral bodies

<table>
<thead>
<tr>
<th>Factors which influence the potential for spontaneous vertebral body reshaping and restitution of bone density, obviating the need for ostroprosisis therapy</th>
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<tbody>
<tr>
<td>Less Potential</td>
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<tr>
<td>Persistent risk factors</td>
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<tr>
<td>&gt;3 months of steroids</td>
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<tr>
<td>Sub-normal mobility</td>
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<td>Poorly-controlled underlying disease</td>
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<td>Older age***</td>
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<td>Less residual growth potential</td>
</tr>
<tr>
<td>More severe collapse</td>
</tr>
<tr>
<td>Higher fracture grade</td>
</tr>
</tbody>
</table>

**Follow the left side of the algorithm

- 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
  - ≥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

**Follow the right 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 vertebrae after fractures
  - Absence of new low-trauma** vertebral and non-vertebral fractures

* Spine imaging by lateral spine radiograph or “vertebral fracture assessment” (VFA) by DXA
** Low trauma is defined as falling from a standing height or less, at no more than walking speed
*** Older age is defined as ≥8 years in girls or ≥9 years of age in boys

b. 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

- Symptoms of osteoporosis interfering with quality of life
- OR
- Lack of potential for spontaneous (medication-unassisted) recovery

- Back pain
- Bone pain
- Reduced mobility

- Older age
- Moderate or severe vertebral collapse
- Persistence of risk factors

- ≥8 years of age
- ≥9 years of age

- ≥3 months of daily IV or oral steroids
- Sub-normal mobility
- Poorly-controlled underlying disease

Figure 9
203x263 mm (DPI)
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
- 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

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

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)

*Annual maximum initiation doses: pamidronate 4.5 to 9 mg/kg/year, every four months; zoledronic acid 0.05 to 0.1 mg/kg/year, every six months
**Annual maintenance doses: pamidronate 4.5 mg/kg/year, every four months; zoledronic acid 0.025 to 0.05 mg/kg/year, every six months

Figure 10
184x209 mm (DPI)
Multiple Vertebral Fractures in a Previously Well 5-Year-Old Boy with Back Pain, a Manifestation of Pediatric Leukemia

Figure 11
106x118 mm (DPI)
Figure 12
212x179 mm (DPI)