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REVIEW

The management of osteoporosis in children

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Summary
This article reviews the manifestations and risk factors associated with osteoporosis in childhood, the definition of osteoporosis and recommendations for monitoring and prevention. As well, this article discusses when a child should be considered a candidate for osteoporosis therapy, which agents should be prescribed, duration of therapy and side effects.

Abstract
There has been significant progress in our understanding of risk factors and the natural history of osteoporosis in children over the past number of years. This knowledge has fostered the development of logical approaches to the diagnosis, monitoring, and optimal timing of osteoporosis intervention in this setting. Current management strategies are predicated upon monitoring at-risk children to identify and then treat earlier rather than later signs of osteoporosis in those with limited potential for spontaneous recovery. On the other hand, trials addressing the prevention of the first-ever fracture are still needed for children who have both a high likelihood of developing fractures and less potential for recovery. This review focuses on the evidence that shapes the current approach to diagnosis, monitoring, and treatment of osteoporosis in childhood, with emphasis on the key pediatric-specific biological principles that are pivotal to the overall approach and on the main questions with which clinicians struggle on a daily basis. The scope of this article is to review the manifestations of and risk factors for primary and secondary osteoporosis in children, to discuss the definition of pediatric osteoporosis, and to summarize recommendations for monitoring and prevention of bone fragility. As well, this article reviews when a child is a candidate for osteoporosis therapy, which agents and doses should be prescribed, the duration of therapy, how the response to therapy is adjudicated, and the short- and long-term side effects. With this information, the bone health clinician will be poised to diagnose osteoporosis in children and to identify when children need osteoporosis therapy and the clinical outcomes that gauge efficacy and safety of treatment.

Keywords Bisphosphonates · Bone density · Bone fragility · Denosumab · Diagnosis · Monitoring · Osteoporosis · Treatment · Vertebral fractures

Abbreviations

ALL	Acute lymphoblastic leukemia
AFF	Atypical femur fractures
AN	Anorexia nervosa
BMD	Bone mineral density
BMAD	Bone mineral apparent density
BTM	Bone turnover markers
CTx	Collagen type I cross-linked C-telopeptide
DMD	Duchenne muscular dystrophy
DXA	Dual energy X-ray absorptiometry
GC	Glucocorticoid(s)
ISCD	International Society for Clinical Densitometry
IV	Intravenous
LS	Lumbar spine
NTx	Collagen type I cross-linked N-telopeptides
OI	Osteogenesis imperfecta

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ONJ	Osteonecrosis of the jaw
PINP	Procollagen type I N-terminal propeptide
pQCT	Peripheral quantitative computed tomography
PTH	Parathyroid hormone
SD	Standard deviation
SDI	Spinal deformity index
VF	Vertebral fracture(s)
VFA	Vertebral fracture assessment (by DXA)

Introduction

Once considered a disease of the aging, osteoporosis is now recognized as an important dimension of clinical care in children with genetic disorders predisposing to bone fragility and in children with serious acute and chronic illnesses. At the same time, approaches to the management of osteoporosis during the pediatric years have been made challenging by a number of factors, including the impact of variable growth rates and tempos of puberty on size-dependent bone mineral density (BMD) testing, distinguishing pathological fractures from those sustained during the course of normal childhood development, and the fact that informative, well-designed intervention trials are themselves a hurdle due to limitations such as smaller sample sizes in pediatric compared to adult studies.

While many principles from the adult osteoporosis literature can be adapted to children, the development of the mature skeleton is nevertheless a complex, multi-decade process that gives rise to unique considerations when embarking on when and how to treat younger patients. Some of these unique differences have been unearthed through long-term natural history studies using standard, widely available evaluative tools, while others have been demonstrated through more sophisticated methods such as peripheral quantitative computed tomography (pQCT) and transiliac bone histomorphometry. Knowledge of these pediatric-specific principles and their biological underpinnings is essential in order to make logical management decisions in the young.

The purpose of this article is to review evidence that shapes the current approach to diagnosis, monitoring, and management of osteoporosis in childhood, with particular emphasis on the key biological principles that are pivotal to the overall approach and on the main questions with which clinicians struggle on a daily basis. The scope of this article spans review of the specific disorders and risk factors associated with osteoporosis in childhood, the clinical manifestations of osteoporosis, issues in the definition and the diagnosis, and recommendations for monitoring and prevention in at-risk children. As well, this article discusses when a child is a candidate for osteoporosis therapy, which agents and doses should be prescribed, the duration of therapy, how the response to therapy should be adjudicated and side effects. With this information, the bone health clinician will be poised to identify which children should be targeted for osteoporosis therapy and the clinical outcomes that effectively gauge efficacy and safety.

Disorders and mechanisms associated with childhood osteoporosis

As highlighted in recent reviews [1–4], childhood osteoporosis is typically divided into primary and secondary causes, with osteogenesis imperfecta (OI) representing the prototypical primary osteoporosis of childhood. There is a growing list of secondary pediatric osteoporoses (i.e., osteoporosis caused by underlying diseases and/or their treatment), with most falling into two broad categories: glucocorticoid (GC)-treated diseases and disorders which compromise normal weight-bearing and mobility. A list of the most common causes of primary bone fragility disorders (and their implicated genes, proteins, and phenotypic features) is provided in Table 1. A list of the secondary osteoporotic conditions of childhood is provided in Table 2.

Primary osteoporosis

Among the most exciting recent developments in the pediatric bone health field has been the elucidation of genes implicated in heritable bone fragility disorders. While the phenotypic heterogeneity in congenital bone fragility has been known for years [5], the spectrum of the genetic basis has only recently come to the fore. Most cases of congenital bone fragility are still due to mutations in the coding regions of the type I collagen genes (*COL1A1* and *COL1A2*, classically referred to as OI types I, II, III, and IV based on disease severity); however, over a dozen additional genetic causes have been described with novel pathobiology and often discrete clinical features [6, 7] (Table 1). In many cases, heritable bone fragility is suggested by the family history or typical physical stigmata (blue sclerae, dentinogenesis imperfecta). However, these findings are not universal even in the presence of type I collagen mutations [8]. In practical terms, the diagnosis of OI remains a possibility in any child with recurrent fractures once a secondary cause has been ruled out (Fig. 1).

Secondary osteoporosis

Advances in pediatric care have led to significant improvements in cure rates for acute disorders such as childhood leukemia [9] and in longevity for chronic disabling conditions such as Duchenne muscular dystrophy (DMD) [10]. With improved outlooks for such children, there is increasing focus on long-term sequelae and quality of life. Despite advances in chemotherapy and disease-modifying interventions, GC therapy remains the mainstay of treatment for many serious illnesses, in the first few years of the illness for disorders such as leukemia and rheumatic conditions [11, 12] and for decades in boys with DMD [13]. In recent years, the use of GC-sparing

Table 1 Genetic causes and clinical features of bone fragility in childhood

Inheritance and Pathogenesis	Diagnosis, Gene, Protein	Clinical Features
A. *Causes of bone fragility due to a type 1 collagenopathy*		
Autosomal Dominant		
1. Nonsense or frameshift mutations causing premature termination of the COL1A1 coding sequence (also called haploinsufficiency; typically associated with a mild phenotype) 2. Glycine missense mutations in COL1A1 or COL1A2 causing type I collagen structural defects (mild to severe phenotypes)	**Diagnosis**: OI **Genes**: *COL1A*, *COL1A2* **Protein**: alpha 1 and 2 chains of type I collagen	Variable severity (mild to perinatal lethal) and variable clinical features. The following may be present: grey or blue sclerae, dentinogenesis imperfecta, scoliosis, triangular facies, limb deformity, wormian bones
Autosomal Recessive		
1. Mutations in chaperone complexes involved in the initiation of type I collagen chain recognition and helical folding	**Diagnosis**: OI **Gene**: *CRTAP* **Protein**: Cartilage-associated protein	Moderate, severe or perinatal lethal, rhizomelia, normal sclerae, coxa vara, early lower limb deformity
	Diagnosis: OI **Gene**: *LEPRE1* **Protein**: Prolyl-3-hydroxlase 1 (P3H1)	Perinatal lethal or severe, white sclerae, bulbous metaphyses, severe growth restriction
	Diagnosis: OI **Gene**: *PPIB* **Protein**: Cyclophyllin B (CyPB)	Moderate, severe or perinatal lethal, growth failure, normal sclerae and teeth
2. Mutations in genes which encode proteins involved in the late stage of type I procollagen quality control, directing final folding and transit from the endoplasmic reticulum to the Golgi	**Diagnosis**: OI **Gene**: *SERPINH1* **Protein**: Heat-shock protein 47 (HSP47)	Severe, triangular facies, blue sclerae, early leg deformity, dentinogenesis imperfecta
	Diagnosis: OI **Gene**: *FKBP10* **Protein**: FK506 binding protein (FKBP65)	Moderate to severe, vertebral fractures, variable dentinogenesis imperfecta and joint contractures
3. Mutations which interfere with late stage type I collagen modification and cross-link formation	**Diagnosis**: OI **Gene**: *SPARC* (*osteonectin*) **Protein**: Secreted protein, acidic and rich in cysteine (SPARC)	Moderate to severe, vertebral fractures, kypho-scoliosis, white sclerae, no dentinogenesis imperfecta, hypotonia, joint hyperlaxity
	Diagnosis: Bruck Syndrome **Gene**: *PLOD2* **Protein**: Lysyl hydroxylase 2 (LH2)	Moderate to severe, vertebral fractures, contractures, normal teeth
4. Mutations which inhibit type I collagen c-propeptide cleavage	**Diagnosis**: OI **Gene**: *BMP1* **Protein**: Bone morphogenetic protein 1 (BMP1)	Moderate to severe, vertebral, fractures, normal teeth, variable sclerae, hypotonia
B. *Causes of bone fragility due to mutations in genes unlinked to type I collagen (involved in bone formation, differentiation and mineralization)*		
1. *Autosomal dominant*	**Diagnosis**: OI **Gene**: *IFITM5* **Protein**: Bone-restricted Ifitm-like (BRIL)	Moderate to severe, hypertrophic callus, calcification of the interosseous membrane of the forearm and leg, white sclerae, lack of wormian bones
2. *Autosomal recessive*	**Diagnosis**: OI **Gene**: *SP7* (*Osterix*) **Protein**: Transcription factor Sp7 (SP7/Osterix)	Moderate to severe, delayed dental eruption, no dentinogenesis imperfecta, normal hearing and sclerae
	Diagnosis: OI **Gene**: *SERPINF1* **Protein**: Pigment-epithelium derived factor (PEDF)	Moderate to severe, normal sclerae and teeth, limb deformity, osteomalacia with looser's zones, alkaline phosphatase may be elevated

Table 1 (continued)

Inheritance and Pathogenesis	Diagnosis, Gene, Protein	Clinical Features
	Diagnosis: OI **Gene**:*TMEM38B* **Protein**:Transmembrane protein 38B (TMEM38B)	Moderate to severe, normal teeth, sclerae, and hearing.
	Diagnosis: OI **Gene**: *WNT1* (heterozygotes have a mild phenotype) **Protein**: WNT1	Moderate to severe, vertebral fractures, short stature, blue sclerae in some patients, normal teeth and hearing
	Diagnosis: OI **Gene**:*CREB3L1* (heterozygotes have a mild phenotype) **Protein**: Old astrocyte specifically induced substance (OASIS)	Perinatal lethal, tubular bones with accordion-like broadened appearance, beaded ribs, blue sclerae
C. *Causes of bone fragility associated with specific, named diseases*		
1. *Autosomal dominant*	**Diagnosis**: Cole-Carpenter Syndrome **Gene**: *P4HB* **Protein**: Protein disulfide isomerase (PDI)	Craniosynostosis, ocular proptosis, hydrocephalus, distinctive facial features, blue sclerae, popcorn epiphyses of the lower extremities
	Diagnosis: Ehlers-Danlos Syndrome **Gene**:*COL3A1* **Protein**: Type III procollagen	Fragility of connective tissues, scoliosis, loose joints and skin, easy bruising, “cigarette-paper” scars, fragile blood vessels and body tissues with arterial and gastrointestinal rupture
	Diagnosis: Marfan Syndrome **Gene**: *FBN1* **Protein**: Fibrillin-1	Tall stature, long limbs and digits, joint laxity, scoliosis, ocular and cardiovascular abnormalities
2. *Autosomal recessive*	**Diagnosis**: Homocystinuria **Gene**: *CBS* **Protein**: Cystathionine beta-synthase (CBS)	Marfan-like features, myopia, ectopia lentis, thromboembolic events
	Diagnosis: Osteoporosis-Pseudoglioma Syndrome **Gene**: *LRP5* (heterozygotes have a mild bone fragility phenotype with normal vision) **Protein**: LDL receptor related protein 5 (LRP5)	Vertebral fractures, scoliosis, short stature and limb deformities, blindness due to ocular pseudoglioma
	Diagnosis: Spondylo-Ocular Syndrome **Gene**: *XYLT2* **Protein**: Xylosyltransferase 2 (XylT2)	Vertebral fractures (marked platyspondyly with fish bone appearance), enlarged intervertebral spaces, normal height with disproportionate short trunk, thoracic kyphosis, and reduced lumbar lordosis, loss of vision due to retinal detachment, sensorineural hearing loss and cardiac septal defects

Table 2 Disorders linked to secondary osteoporosis in childhood

Chronic illness	Iatrogens
a. Malignancy (leukemia, lymphoma)	a. Glucocorticoids
b. Rheumatologic disorders	b. Methotrexate
c. Anorexia nervosa	c. Cyclosporine
d. Cystic fibrosis	d. Heparin
e. Inflammatory bowel disease	e. Radiotherapy
f. Renal disease	f. GnRH agonist
g. Transplantation	g. Medroxyprogesterone acetate (long-term use)[a]
h. Other: primary biliary cirrhosis, cyanotic congenital heart disease, thalassemia, malabsorption syndromes, celiac disease, epidermolysis bullosa	h. L-Thyroxine suppressive therapy
	i. Anticonvulsants
Neuromuscular disorders	Inborn errors of metabolism
a. Cerebral palsy	a. Lysinuric protein intolerance
b. Rett syndrome	b. Glycogen storage disease
c. Duchenne muscular dystrophy	c. Galactosemia
d. Spina bifida	d. Gaucher disease
e. Spinal muscular atrophy	
Endocrine and reproductive disorders	
a. Disorders of puberty	
b. Turner syndrome	
c. Growth hormone deficiency	
d. Hyperthyroidism	
e. Hyperprolactinemia	
f. Athletic amenorrhea	
g. Cushing syndrome	
h. Type 1 diabetes	

[a] Long-term use (>10 years) has been associated with reductions in BMD among adult women [132]

biological agents has led to improved health outcomes for children with Crohn's disease [14, 15] and juvenile arthritis [16]; not surprisingly, evidence for a positive effect of these agents on skeletal health has been demonstrated in a number of contemporary studies [15, 17–19].

A recent census of our bone health clinic (housed in a general, tertiary pediatric hospital) revealed that out of 89 patients with chronic illnesses and a history of low-trauma fractures necessitating osteoporosis therapy, 40 % had GC-naive neuromuscular disorders (cerebral palsy, congenital myopathy), 27 % had GC-treated DMD, 24 % had other GC-treated disorders (rheumatic disorders, Crohn's disease, myasthenia gravis), and 9 % held diagnoses of leukemia or other cancers. These data provide insight into the systemic illness groups likely to present to a pediatric bone health clinic with low-trauma fractures requiring osteoporosis intervention.

Manifestations, frequency, and clinical predictors of osteoporotic fractures

Manifestations of osteoporosis: vertebral fractures

A number of studies have highlighted that vertebral fractures (VF) are an important yet under-recognized manifestation of osteoporosis in children. This is particularly true in children with GC-treated disorders given the predilection of GC therapy to adversely impact the trabecular-rich spine [20, 21]. In GC-treated illnesses such as rheumatic disorders, nephrotic syndrome, leukemia, and DMD, the prevalence of VF ranges from 7 to 32 % [21–24] and the 12-month incidence from 6 to 16 % [25–27] depending upon the underlying disease. The peak annual incidence in children with GC-treated rheumatic disorders and leukemia occurs at 1 year, in line with the time during which annual GC exposure is maximal for most patients with these conditions [11, 12]. At the same time, children with chronic diseases who are GC naive are not exempt from spine fragility, since vertebral collapse has been shown to occur in 25 % of children with motor disabilities [28].

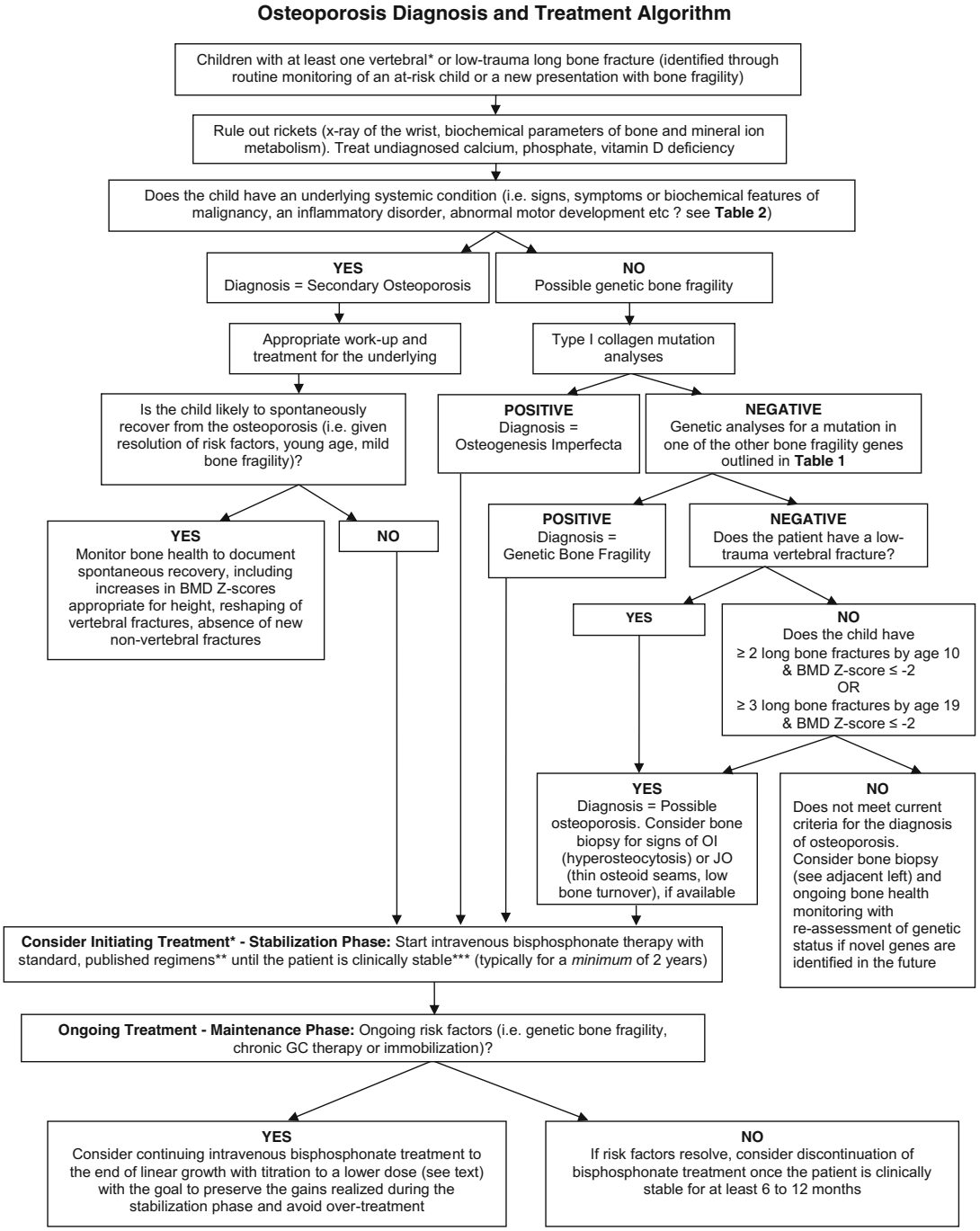
VF often go undetected in children for two main reasons. First, VF can be asymptomatic [22–27], even in the face of moderate to severe collapse [11, 22]. Secondly, routine surveillance with a periodic spine X-ray has not historically been signaled an important component of osteoporosis monitoring. However, a recent position statement by the International Society for Clinical Densitometry (ISCD) proposed that monitoring beyond BMD is needed in at-risk children, since the diagnosis of osteoporosis in children with at least one VF no longer requires BMD criteria [29]; furthermore, the position statement acknowledges that BMD Z-scores above −2 standard deviations (SD) do not preclude increased vertebral and non-VF risk.

Manifestations of osteoporosis: non-vertebral fractures

Low-trauma non-VF in childhood are observed most frequently at the femur, tibia, forearm, humerus, feet, and ankles [21, 30, 31]. Long bone fractures are the most frequent and disabling of the non-VF in childhood, while hip fractures occur rarely and should prompt consideration of serious underlying diseases such as childhood leukemia [32]. Looser zones, also known as "insufficiency fractures," may be mistaken for osteoporotic fractures; however, they represent the distinctly different process of osteomalacia, defined histomorphometrically as an increase in osteoid thickness associated with prolongation of the mineralization lag time. Looser zones appear as incomplete cracks in the cortex at the ribs, scapulae, medial shafts of long bones, and pubic rami. In such cases, the patient requires an assessment for a disorder of calcium and/or phosphate metabolism including a hand X-ray (to rule out rickets if the growth plate is still active) and biochemical parameters of bone and mineral ion metabolism (Fig. 1).

The frequency and clinical predictors of fractures in at-risk children

In recent years, there has been an effort to delineate disease-specific risk factors for osteoporosis through natural history studies, by assessing the precise relationship between various



* **Typical treatment indications**: Low-trauma long bone or vertebral fractures. Additional treatment considerations include the impact of the fractures on quality of life and lack of potential for spontaneous (i.e. medication-unassisted) recovery due to persistent osteoporosis risk factors

** **IV bisphosphonate starting doses (see text and Table 4 for details):** Pamidronate *maximum* 9 mg/kg/year in divided doses, Zoledronic acid *maximum* 0.1 mg/kg/year in divided doses, or Neridronate *maximum* 6 mg/kg/year in divided doses. See text for use of and titration to lower doses

*** **Clinically stable includes:**

- Absence of new VF in previously normal vertebral bodies and absence of further loss of vertebral height at sites of previous fractures
- Reshaping of vertebral fractures
- Absence of new non-vertebral fractures, bone and back pain
- Improved mobility, increases in spine BMD Z-score appropriate for height

Abbreviations: BMD = bone mineral density; GC = glucocorticoid; OI = osteogenesis imperfecta; JO = juvenile osteoporosis, VF = vertebral fractures; non-VF = non-vertebral fractures

Fig. 1 Algorithm of the approach to the diagnosis and treatment of children with fractures due to osteoporosis

illness-related factors and fractures, as well as the relationship between measurable indicators of bone health and fractures (such as BMD and back pain, see Table 3). These studies have provided robust results that fine-tune the clinician's ability to identify the at-risk child.

Vertebral fractures

As shown in Table 3, a number of studies have been sufficiently powered to assess clinical predictors of prevalent or incident (new) VF in univariate or multivariable models. Studies which show significant differences in relevant clinical parameters between those with and without VF have also been included in Table 3. Most studies have been retrospective or cross-sectional; relatively few studies have assessed the frequency of new VF in relation to the evolving (longitudinal) clinical course of the child.

From these studies, a number of clinically useful themes have emerged. First, GC exposure is a consistent predictor of both prevalent and incident VF, an observation that is not surprising given clinical experience and the known osteotoxicity of GC therapy. Both cumulative and average daily dose predict VF in a number of different diseases as outlined in Table 3, as well as GC dose intensity ("pulse therapy") in children with leukemia [11]. Secondly, leukemia studies have shown that prevalent VF around the time of GC initiation are highly predictive of future fractures, a phenomenon referred to in adults as "the VF cascade" [11, 25]. In fact, even mild (grade 1) VF independently predict future fractures, highlighting the importance of identifying early signs of vertebral collapse [11, 25]. While back pain predicted prevalent VF in two studies of children with GC-treated leukemia and rheumatic disorders [22, 24], pain did not predict new VF [11, 12]. The message arising from these data is that a lack of back pain does not rule out the presence of VF in at-risk children.

The fact that prevalent VF around the time of GC initiation predict future VF draws attention to the clinical importance of understanding the skeletal phenotype early in the child's disease course. In children with GC-treated rheumatic disorders, discrete clinical features in the first year were also independent predictors of future VF, including increases in disease activity scores in the first 12 months of GC therapy as well as increases in body mass index and decreases in lumbar spine (LS) BMD Z-scores, both in the first 6 months of GC therapy [12]. In children with solid organ transplantation, older age was also a consistent predictor of increased VF risk [33–36].

Non-vertebral fractures

Predictors of non-VF fractures in children with chronic illnesses are also outlined in Table 3, most of which are cross-sectional or retrospective. Loss of ambulation, anticonvulsant medication, and reductions in BMD at various skeletal sites are among the most consistent predictors of non-VF in this setting. An important observation making use of lateral distal femur BMD, a frequent site of fracture in children with neuromuscular disorders, is that every 1 SD reduction in BMD Z-score at this site was associated with a 15 % increase in lower extremity fractures [37].

Spontaneous recovery from osteoporosis in the absence of osteoporosis therapy

The pediatric skeleton is a dynamic structure with the distinct capability not only to reclaim BMD lost during transient bone health insults but to reshape fractured vertebral bodies through the process of skeletal modeling. Both indices are important measures of recovery in children, either spontaneously or following osteoporosis therapy (i.e., bisphosphonate treatment). Vertebral body reshaping appears to be growth-mediated, since it has never been unequivocally reported in adults [38]. We hypothesize that bisphosphonate therapy does not directly bring about reshaping but rather has a permissive effect by optimizing BMD in order to prevent further collapse [39].

The disease that has been best-studied for signs of recovery from skeletal insult in the absence of osteoporosis therapy is acute lymphoblastic leukemia (ALL). This is not surprising, since ALL represents a transient threat to bone health in the majority of patients undergoing contemporary treatment strategies. Mostoufi-Moab et al. [40] assessed children by tibia pQCT and found that trabecular and cortical BMD Z-scores were significantly reduced compared to healthy controls within 2 years postchemotherapy cessation but that significant improvements (on average 0.5 SD) were evident a year later. Cortical dimensions also increased, followed by increases in cortical BMD. Other studies have also shown recovery in bone mass and density in the years following chemotherapy [41, 42]. Lack of BMD restitution is predicted by cranial and spinal radiation, particularly at doses ≥24 Gy [42], although it should be noted that the lower spine BMD among those with radiation exposure appears to arise in part from hormone deficiency-related short stature. Other recognized risk factors for incomplete BMD restitution in ALL include untreated hypogonadism, vitamin D deficiency, hypophosphatemia, low IGF-binding protein-3, and reduced physical activity [43].

The fact that reshaping can occur during leukemia chemotherapy (i.e., during high-dose GC therapy) is hypothesized to result from the saltatory pattern of GC exposure with current treatment protocols (Fig. 2a). Vertebral body reshaping has also been observed in our clinic among children with rheumatic disorders post-GC cessation, though not previously reported (Fig. 2b). On the other hand, older children who have insufficient residual growth potential can be left with permanent vertebral deformity after vertebral collapse (Fig. 2c). The long-term consequences of permanent deformity remain unstudied; however, reports in adults indicate compromised

Table 3 Risk factors for fractures in children with specific disorders

Author (reference)	Disease	No. of patients	Study design	Fracture location (with assessment method for vertebral fractures)[a]	Fracture prevalence and/or incidence (%)	Clinical predictors of prevalent or incident VF from univariate or multivariable models (with effect size and 95 % CI) or from statistical tests comparing children with and without fractures
Predictors of prevalent fractures (vertebral and nonvertebral fractures combined)						
Henderson et al. [37]	Cerebral palsy or muscular dystrophy	619	Cross-sectional	NR	•Prevalence 27 % (at an average age of 11.8 years)	•↓ Distal femur BMD (proximal to growth plate) Z-score: RR = 1.09 (1.04, 1.13)[b] •↓ Distal femur BMD (transition from metaphysis to diaphysis) Z-score: RR = 1.06 (1.02, 1.10)[b] •↓ Distal femur BMD (diaphyseal cortical bone) Z-score: RR = 1.15 (1.09, 1.22)[b]
Fung et al. [191]	Thalassemia or treated sickle cell disease	136	Prospective, natural history comparative study	Upper and lower extremities and other sites	•Prevalence 17 % (in patients 12 to 18 years of age)	•Thalassemia versus sickle cell disease: OR = 2.3 (1.2, 4.6)[b, c] •↑ Male: OR = 2.6 (1.5, 4.5)[b, c] •↑ Age
Predictors of prevalent fractures (nonvertebral fracture only)						
Dosa et al. [192]	Spina bifida	221	Historical cross-sectional	Upper and lower extremity and other site	•Prevalence 20 %[c] (in patients 2 to 58 years of age) •Annual incidence 2.6 % (in patients 2 to 18 years of age)	Predictors of prevalent and incident fractures combined: •↑ Spine defect level: RR = 1.65 (1.09, 2.50)[b, c] •↑ Age: RR = 1.03 (1.00, 1.07)[b, c]
Predictors of prevalent fractures (vertebral fracture only)						
Nakhla et al. [193]	Rheumatic diseases[d]	90	Cross-sectional	•Vertebrae •Lateral spine X-ray[a] (1)	•Prevalence 19 % (at a median age of 13.1 years)	•Male: OR = 6.04 (2.85, 12.81)[b] •↑ Cumulative GC (g/kg): OR = 4.50 (1.42, 14.28)[b] •↑ BMI Z-score: OR = 1.49 (1.05, 2.09)[b]
Valta et al. [35]	Renal transplant[d]	106	Cross-sectional	•Vertebrae •DXA and lateral spine X-ray[a] (2)	•Prevalence 8 % (5.1 years after transplant)	•↑ Age at the time of study •↑ Time since transplant
Valta et al. [34]	Liver transplant[d]	40	Cross-sectional	•Vertebrae •DXA and lateral spine X-ray[a] (2)	•Prevalence 18 % (7 years after transplant)	•↑ Age at transplant •Recently transplanted •↑ BMI •↑ Whole body fat percentage •↓ Cumulative weight-adjusted GC dose •↓ LS BMD Z-score •↓ Proximal femur BMD Z-score •↓ TB BMD Z-score
Helenius et al. [33]	Solid organ transplant[d]	40	Cross-sectional	•Vertebrae •DXA and lateral spine X-ray[a] (2)	•Prevalence 35 % (11.2 years after transplant)	•Male •Treated for acute rejection
Halton et al. [22]	Leukemia[d]	186	Cross-sectional	•Vertebrae •Lateral spine X-ray[a] (1)	•Prevalence 16 % (at a median of 18 days from GC initiation)	•Back pain: OR = 4.7 (1.5, 14.5)[b] •↓ % cortical area Z-score: OR = 2.0 (1.0, 3.2)[b] •↓ LS BMD Z-score: OR = 1.8 (1.1, 2.9)[b]

Table 3 (continued)

Author (reference)	Disease	No. of patients	Study design	Fracture location (with assessment method for vertebral fractures)[a]	Fracture prevalence and/or incidence (%)	Clinical predictors of prevalent or incident VF from univariate or multivariable models (with effect size and 95 % CI) or from statistical tests comparing children with and without fractures
King et al. [21]	Duchenne muscular dystrophy[d]	143	Retrospective chart review	•Vertebrae •Spine X-ray •Method not specified	•Prevalence 32 % (mean duration of GC therapy 8 years)	•GC treatment ≥1 year
Feber et al. [23]	Nephrotic syndrome[d]	80	Cross-sectional	•Vertebrae •Lateral spine X-ray[a] (1)	•Prevalence 8 % (within the first month following GC initiation)	•Vitamin D daily intake <50 % DRI
Ben Amor et al. [6]	Osteogenesis imperfecta	58	Cross-sectional	•Vertebrae •Lateral spine X-ray[a] (1)	•Prevalence 71 % (at an average age of 7.4 years)	•↓ LS BMD Z-score: OR = 0.4 (0.2, 0.9)[b] •Male: OR = 6.6 (1.5, 28.3)[b]
Engkakul et al. [194]	Thalassemia syndromes	150	Retrospective chart review and cross-sectional	•Vertebrae •Lateral spine X-ray[a] (1)	•Prevalence 13 %[c] (at a median age of 15.7 years)	•Severe thalassemia: OR = 5.7 (2.0, 16.8)[b] •Age (20 years or older): OR = 5.0 (1.7, 14.0)[b]
Mayranpaa et al. [195]	Recurrent fractures	66	Prospective, observational	•Vertebrae •Lateral spine X-ray[a] (2)	•Prevalence 29 % (at an average age of 10.7 years)	•↓ Serum 25OHD •Fewer long bone fractures per child •↓ LS BMD Z-score
Predictors of incident fractures (vertebral and nonvertebral fractures combined)						
Helenius et al. [33]	Solid organ transplant[d]	196	Retrospective chart review plus 10 years prospective observation after transplant	•Upper and lower extremity, vertebrae, and other site •DXA and lateral spine X-ray[a] (2)	•Incidence 9.2 per 100 person-years (on average 9.2 years from transplant) •Cumulative incidence 40 %	•Sex (male versus female): HR = 2.15 (1.22, 3.81)[b] •Age at the time of transplant (5–12 versus 0–4 years): HR = 1.80 (1.01, 3.20)[b] •Age at the time of transplant (13–20 versus 0–4 years): HR = 2.02 (1.07, 3.83)[b] •Transplant organ (liver versus kidney): HR = 1.78 (1.01, 3.14)[b] •Transplant organ (heart versus kidney): HR = 1.90 (0.93, 3.92)[b]
Predictors of incident fractures (nonvertebral fracture only)						
Helenius et al. [33]	Solid organ transplant[d]	196	Retrospective chart review plus 10 years prospective observation after transplant	•Upper and lower extremity and other site •DXA and lateral spine X-ray[a] (2)	•Incidence 3.8 per 100 person-years (on average 9.2 years from transplant) •Cumulative incidence 27 %	•Fracture before transplant (yes versus no): RR = 4.61 (1.12, 18.90) •Sex (male versus female): RR = 2.14 (1.17, 3.93) •Age at the time of transplant (5–12 versus 0–4 years): RR = 1.95 (0.98, 3.89) •Age at the time of transplant (13–20 versus 0–4 years): RR = 2.24 (1.01, 5.00)
Predictors of incident fractures (vertebral fracture only)						
Cummings et al. [11]	Leukemia[d]	186	48 months prospective, observational	•Vertebrae •Lateral spine X-ray[a] (1)	•Incidence 8.7 per 100 person-years (in the first 4 years after diagnosis) •Cumulative incidence 26.4 %	•Prevalent VF (mild versus none): HR = 4.2 (1.9, 9.6)[b] •Prevalent VF (moderate/severe versus none): HR = 6.2 (3.4, 11.4)[b] •↑ Average daily GC (10 mg/m^2): HR = 5.9 (3.0, 11.8)[b] •↓ LS BMD Z-score at the time of VF assessment: HR = 1.6 (1.2, 2.2)[b] •↓ Age: HR = 1.1 (1.0, 2.2)[b] •↑ Recent[e] average daily GC (10 mg/m^2): HR = 5.1 (2.8, 9.5)[b] •↑ Recent[e] GC dose intensity (10 mg/m^2): HR = 1.2 (1.1, 1.4)[b]
Alos et al. [25]	Leukemia[d]	155	12 months prospective, observational	•Vertebrae •Lateral spine X-ray[a] (1)	•Incidence 16 % (at 12 months following diagnosis)	•Prevalent VF (yes versus no): OR = 7.30 (2.30, 23.14)[b] •Prevalent VF (mild versus none): OR = 7.6 (1.8, 31.8)[b] •Prevalent VF (moderate/severe versus none): OR = 7.0 (1.6, 30.2)[b] •↓ LS BMD Z-score: OR = 1.8 (1.2, 2.7)[b]

Table 3 (continued)

Author (reference)	Disease	No. of patients	Study design	Fracture location (with assessment method for vertebral fractures)[a]	Fracture prevalence and/or incidence (%)	Clinical predictors of prevalent or incident VF from univariate or multivariable models (with effect size and 95 % CI) or from statistical tests comparing children with and without fractures
LeBlanc et al. [12]	Rheumatic diseases[d]	134	36 months prospective, observational	•Vertebrae •Lateral spine X-ray[a] (1)	•Incidence 4.4 per 100 person-years (in the 3 years following GC initiation) •Cumulative incidence 12.4 %	•↑ Average daily GC dose (0.5 mg/kg): HR = 2.0 (1.1, 3.5)[b] •↑ VAS score, baseline to 12 months: HR = 1.4 (1.1, 1.7)[b] •↑ BMI Z-score in the first 6 months preceding each annual VF assessment: HR = 3.2 (1.6, 6.5)[b] •↓ LS BMD Z-score, baseline to 6 months: HR = 3.0 (1.1, 8.1)[b] •↑ Duration (month) of GC therapy in the preceding 12 months of each VF assessment: HR = 1.2 (1.1, 1.4)[b]
Rodd et al. [27]	Rheumatic diseases[d]	117	12 months prospective, observational	•Vertebrae •Lateral spine X-ray[a] (1)	•Incidence 5 % (at 12 months following GC initiation)	•↑ BMI Z-score, study entry to 6 months •↑ Weight Z-score, study entry to 6 months •↓ LS BMD Z-score, study entry to 6 months •LS BMD Z-score <−2.0 at 12 months •↑ Cumulative GC •↑ Average daily GC
Helenius et al. [33]	Solid organ transplant[d]	196	Retrospective chart review plus 10 years prospective observation after transplant	•Vertebrae •DXA and lateral spine X-ray[a] (2)	•Incidence 5.7 per 100 person-years (on average 9.2 years after transplant) •Cumulative incidence 18 %	•BMI ≥19 kg/m^2 at transplant: RR = 4.30 (1.26, 9.97) •Age at the time of transplant (5–12 versus 0–4 years): RR = 2.32 (1.07, 5.05) •Age at the time of transplant (13–20 versus 0–4 years): RR = 4.16 (1.60, 10.81)
Vautour et al. [36]	Renal transplant[d]	86	Retrospective chart review plus 15 years prospective follow-up	•Vertebrae •Lateral spine X-ray[a] (3)	•Cumulative incidence 20 %[c] (in the 15 years following transplant)	•↑ Age: HR = 1.8 (1.2, 2.7)[b] •Prior diagnosis of osteoporosis: HR = 9.5 (2.6, 35)[b]

Studies were included in the table if prevalence or incidence data were available and risk factors for prevalent or incident fractures were described. Studies which show significant differences in relevant clinical parameters between those with and without fractures were also included

BMI body mass index, *CI* confidence interval, *DRI* dietary reference intake, *DXA* Dual-energy X-ray absorptiometry, *GC* glucocorticoid(s), *HR* hazard ratio, *LS BMD* lumbar spine bone mineral density, *OR* odds ratio, *TB BMD* total body BMD, *NR* not reported

[a] Assessment methods for vertebral fractures reported in these studies (see: (1) Genant semiquantitative method, Genant et al. [50]; (2) method reported by Makitie et al. [190]; (3) method reported by Eastell et al. [52])

[b] Magnitude of association was obtained from multivariable models

[c] This result was based on a cohort with both children and adults

[d] Steroid-treated disease

[e] Recent: 12 months preceding VF assessment

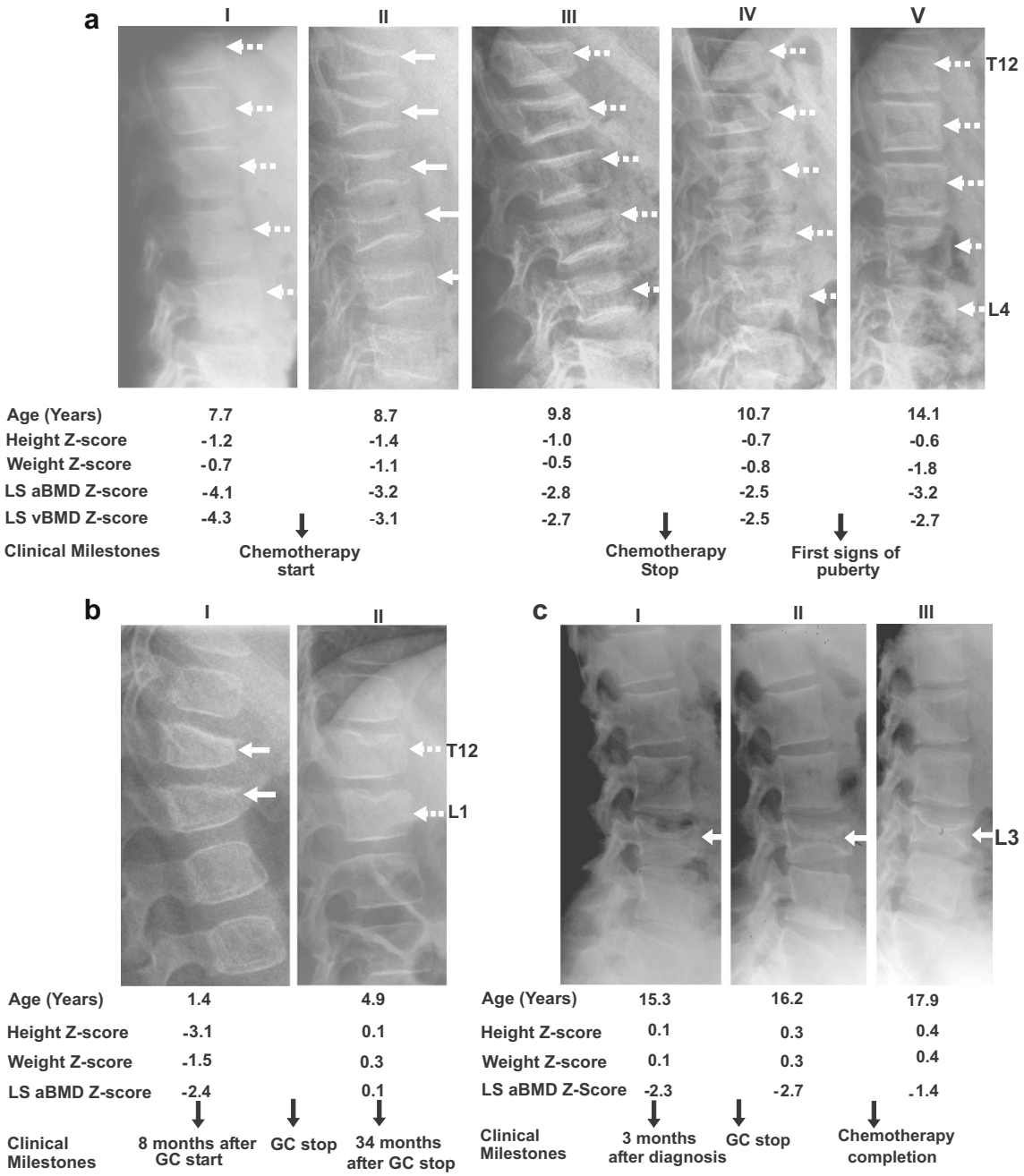


Fig. 2 **a** *I* Lateral spine radiographs in a 7.7-year-old girl at diagnosis with pre-B acute lymphoblastic leukemia showing a normal spine radiograph. *II* Vertebral fractures after 1 year of chemotherapy, as follows: grade 3 (severe) wedge fractures at T12 and L1; grade 2 (moderate) biconcave fracture at L2; grade 3 (severe) biconcave vertebral fractures at L3 and L4. *III–V* These panels show stages in vertebral body reshaping with a "bone within bone" appearance during and after chemotherapy, in the absence of bone-specific (bisphosphonate) therapy. **b** *I* Lateral spine radiographs showing vertebral fractures in a toddler with systemic-onset juvenile idiopathic arthritis. Grade 2 vertebral fractures at T12 and L1 on GC therapy at 1.4 years of age. *II* At 4.9 years of age, she has almost complete recovery of vertebral height ratios with the typical "bone within bone" appearance, in the absence of bone-specific (bisphosphonate) therapy. **c** *I* Lateral spine radiographs showing a grade 3 (severe) fracture at L3 in a 15.3-year-old girl with pre-B acute lymphoblastic leukemia 3 months after diagnosis. At diagnosis, she had already attained final adult height. *II*, *III* Lack of reshaping due to fused epiphyses and absence of endochondral bone formation. *vBMD* = volumetric BMD; *aBMD* = areal BMD. Solid arrows indicate vertebral bodies that have been fractured. Hatched arrows indicate vertebral bodies undergoing reshaping

quality of life due to pain and functional limitation [44, 45]. Whether the same is true later in life following permanent vertebral deformity after childhood VF merits further study.

To understand the vertebral body reshaping phenomenon further, the Canadian STeroid-Induced Osteoporosis in the Pediatric Population (STOPP) Consortium has explored

determinants of complete versus incomplete reshaping in bisphosphonate-naive ALL (quantified by a decrease in a positive spinal deformity index (SDI) [46] by 100 % in the 6 years following diagnosis). Preliminary analyses suggest that many children reshape following VF in ALL but those with moderate or severe vertebral collapse and those who are older at diagnosis may reshape less frequently. The next question is whether children with VF and persistent bone health threats in the context of other diseases such as GC-treated DMD can undergo vertebral body reshaping without bisphosphonate therapy. At the present time, there are no published reports to suggest that they do, a fact that is corroborated by our own clinical experience.

Bone health monitoring in at-risk children

Monitoring goals and candidates

The ultimate goal of monitoring is to identify high-risk patients for intervention that will prevent the first fracture. However, lack of available data to support such primary prevention has instead led to monitoring that identifies early rather than late signs of osteoporosis, followed by bone-active treatment in those with limited potential for spontaneous recovery (including vertebral body reshaping). This is in line with a secondary prevention approach, which seeks to mitigate the progression of the osteoporosis following identification in its earlier stages.

Two important observations have shifted monitoring away from a BMD-centric to a more functional approach: (1) The use of a BMD Z-score threshold to identify a child is problematic due to variability in the Z-scores generated by the different available normative databases [47–49], and (2) asymptomatic VF can occur at BMD Z-scores >−2, thereby requiring imaging surveillance for VF detection. Other functional outcomes should also be tracked during monitoring including history of non-VF, growth, pubertal status, pain, mobility, muscle strength, and the potential for spontaneous recovery (vertebral body reshaping and bone density restitution). BMD remains a vital part of the bone health monitoring approach but as an adjuvant tool to chart the child's BMD trajectory, thereby signaling a child who is losing ground and therefore at increased risk for fractures, or who is showing signs of recovery following a transient bone health threat (potentially obviating the need for osteoporosis treatment).

Patients expected to be GC-treated for ≥3 months should be considered for a baseline spine radiograph (or high quality dual energy X-ray absorptiometry (DXA)-based VF assessment (VFA), if available) at the time of GC initiation. Three months or more is the recommended cut-off since the earliest incident VF reported after GC initiation in children is at 4 months [27]. Children meeting the criteria for baseline spine imaging should also undergo a follow-up radiograph at 12 months, since this is the time point with the highest annual incidence of VF in many GC-treated children [11, 27]. Annual to biannual imaging for VF is advised thereafter for those with ongoing GC exposure. The predictors of VF outlined in Table 3 can facilitate the decision around the frequency of VF follow-up assessments beyond 12 months.

Among children with other risk factors for bone fragility apart from GC exposure (Tables 1, 2, and 3), the same principles apply; that is, the patient should be assessed for both non-VF and VF since GC-naive children with mobility issues and genetic bone fragility can also develop VF [6, 28]. In youth with impaired mobility due to cerebral palsy and congenital myopathies, a spine radiograph is recommended at the latest by about 6 to 8 years of age and then at intervals thereafter until the end of growth, or sooner in the presence of back pain. Monitoring is recommended to start by this time since treatment should be initiated *before* there is insufficient residual growth potential for vertebral body reshaping.

Since BMD is useful as a serial measurement to assist the clinician in understanding the child's overall bone health trajectory and in making logical decisions about the need for ongoing monitoring, discharge from bone health care or intervention, it is recommended that a BMD is carried out at least as frequently as spine radiographs according to the above guidelines, with assessments every 6 months in those children at greatest risk [4, 29].

Axial skeletal health: vertebral fracture detection methods and imaging modalities

The most widely used tool for the assessment of VF in both children and adults is the Genant semiquantitative method [50, 51]. According to the Genant method, the definition of a VF is ≥20 % loss in vertebral height ratio regardless of the VF morphology. VF are subjectively graded by trained readers according to the magnitude of the reduction in vertebral body height ratios, without direct measurement. Vertebral height ratios are generated when the anterior vertebral height is compared with the posterior height (for an anterior wedge fracture), middle height to the posterior height (biconcave fracture), and posterior height to the posterior height of adjacent vertebral bodies (crush fracture). The Genant scores correspond to the following reductions in height ratios: grade 0 (normal), <20 %; grade 1 fracture (mild), ≥20 to 25 %; grade 2 fracture (moderate), >25 to 40 %; and grade 3 fracture (severe), >40 %. Overall, the Genant semiquantitative method is preferred over quantitative (six-point) vertebral morphometry [52], since it is faster and takes into consideration the expertise

of an experienced reader. In addition, it quantifies the severity of VF (an important predictor of the lack of potential for spontaneous vertebral body reshaping following VF in children). Furthermore, the Genant scoring system permits calculation of the SDI, the sum of the Genant grades along the length of the spine [46]. The SDI is a global index of spine morbidity that is useful clinically and can be used as a continuous outcome variable in research studies [53]. The kappa statistics for intra- and interobserver agreement are similar for children compared to adults using the Genant semiquantitative method [50, 54, 55].

A number of recent studies have provided validity for the Genant approach in children. First, Genant-defined VF show a bimodal distribution from T4 to L4 similar to the known distribution in adults [56–59], with a predilection for the mid-thoracic region (T5 to T8, the site of the natural kyphosis) and the thoracolumbar junction (the site of transition to the natural lordosis) [22, 59]. Secondly, biologically relevant clinical predictors of Genant-defined VF have been identified including back pain, low LS BMD Z-scores, longitudinal declines in LS BMD Z-scores and GC exposure [12, 22, 25]. One of the most important observations to assert the validity in children is that both mild and moderate-severe Genant-defined VF at leukemia diagnosis are robust clinical predictors of new VF over the next 3 years [11, 25].

To date, the most common imaging tool for VF detection in childhood is lateral thoracolumbar spine radiographs. In view of the high radiation exposure from spine radiographs but nevertheless critical need for VF assessments as part of bone health evaluations, nonradiographic imaging techniques have been developed which use the scoring methods described above. The use of DXA to diagnose VF is called VFA (vertebral fracture assessment) with images captured on a lateral spine view. VFA is attractive as an assessment tool given its minimal radiation and the fact that fan-beam technology facilitates the capture of the entire spine on a single image without divergent beam issues due to parallax. Newer DXA machines have a rotating "c-arm" which obviates the need to reposition the patient from the supine to lateral position. Image quality varies significantly depending on the densitometer [60]. Using a Hologic Discovery A machine, Mayranpaa et al. [61] showed low diagnostic accuracy for VFA compared to lateral spine radiographs and poor visibility in children. Pediatric studies on newer DXA machines are presently underway.

Axial skeletal health: transiliac bone biopsies

Iliac crest bone biopsies with tetracycline labeling provide unique diagnostic information about static and dynamic bone properties that cannot be obtained by any other means (i.e., osteoid thickness, bone formation rate, mineralization lag time, and other bone formation and resorption indices) [62]. In practical terms, biopsies are useful in establishing the cause of osteoporosis in special cases such as a child with unexplained bone fragility and negative genetic studies. Idiopathic juvenile osteoporosis has a characteristic histomorphometric appearance—low bone turnover and thin osteoid seams—but clinically may be difficult to distinguish from other forms of osteoporosis such as nondeforming OI without blue sclerae, wormian bones, or a family history [63, 64]. Similarly, patients with OI typically have a histological hallmark (hyperosteocytosis) that is helpful diagnostically in rare cases when studies are falsely negative [63, 64]. At the same time, few clinicians are trained in this technique and so overall, it is a rarely used tool aside from highly specialized clinics.

Axial and appendicular skeletal health: dual energy X-ray absorptiometry

DXA is the most commonly used and widely available technique to measure bone mass and density in children, since it is highly reproducible, inexpensive and confers low radiation exposure. LS and total body less head are the preferred measuring sites [65]; recently, lateral distal femur BMD Z-scores have also been useful in children with neuromuscular disorders who prefer to position on their side [37, 66] (Table 3). BMD raw values are converted to age- and sex-specific SD scores (Z-scores) and require additional interpretation in view of body size, ethnicity, and pubertal staging or skeletal maturity (the latter, by bone age) [67]. Since BMD can be underestimated in children with familial short stature, and children with chronic illnesses may be transiently or permanently short due to the effects of the disease/treatment on linear growth and puberty, adjustment for bone size using a technique such as bone mineral apparent density (BMAD or volumetric BMD, in g/cm^3) [68] or height Z-score-corrected BMD Z-scores [69] is required to avoid underestimation of BMD parameters. BMAD has the advantage that it has been tested for its ability to accurately predict VF [70], whereas height Z-score-corrected BMD Z-scores have not. Lateral distal femur BMD Z-scores predicted non-VF in children with neuromuscular disorders [37]; and furthermore, this assessment method is taken at a clinically relevant site, since children with neuromuscular disorders often fracture at this location. Despite challenges in BMD interpretation due to variable growth rates and timing and tempos of puberty, numerous studies (Table 3) confirm an inverse relationship between BMD and fracture rates, and serial measurements provide additional information about the child's overall bone health trajectory that can inform whether there is a need for ongoing bone health monitoring.

Appendicular skeletal health: peripheral quantitative computed tomography

pQCT at the radius and tibia provides information that cannot be obtained by DXA about musculoskeletal geometry as well as "true" (volumetric) cortical and trabecular BMD. For example, in children with cerebral palsy, it has been shown that smaller bone and cortical cross-sectional area are the main structural defect rather than lower cortical BMD [71]; pQCT studies have also shown that cortical thickness and not density is the main parameter impacted by growth hormone deficiency and treatment [72]. pQCT is particularly useful when DXA studies are precluded due to spine deformity, hip and knee contractures, or metallic hardware. The newest technique, high-resolution pQCT, has the spatial resolution to measure trabecular geometry and microarchitecture. At the moment, pQCT and high-resolution pQCT are research tools in most centers.

Bone turnover markers

Bone turnover markers (BTM) are often measured in children undergoing a bone health assessment or while on osteoporosis therapy. Recently, two markers have been recommended by the International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine [73]: serum procollagen type I N-terminal propeptide (PINP, a marker of bone formation) and serum collagen type I cross-linked C-telopeptide (CTx, a marker of bone resorption), both of which have been studied in healthy children in order to generate reference data [74–77]. These analytes were chosen because of their specificity to bone and relationship to relevant outcomes in adult clinical studies as well as their stability, wide availability, and ease of analysis and procurement.

BTM are influenced by several factors that lead to high intra- and interindividual variability, including age/pubertal stage, gender, time of day, food intake, physical activity, recent fractures, serum 25-hydroxyvitamin D status, assay methods, and sample transport and storage conditions. One of the main factors that have limited their use in children, particularly for those with chronic illness and growth delay, is that BTM are largely a reflection of linear growth and not bone turnover per se. In children, the only available method to determine bone turnover status with certainty is to directly measure bone formation and resorption on trabecular surfaces via transiliac bone biopsy; however, this tool is not in widespread clinical use.

In a recent adult review, BTM were not recommended to diagnose osteoporosis because of weak and inconsistent correlations with BMD and lack of evidence that they independently predict fracture risk [78], a view supported by the ISCD [79]. For adults undergoing monitoring during osteoporosis therapy, fracture risk reduction is independent of pretreatment BTM [80–82]; therefore, pretreatment values should not direct the choice of osteoporosis therapy. During therapy, the evidence from adult clinical trials is still emerging around the definition of a marker response that identifies optimal fracture risk reduction. In women treated with risedronate, the non-VF incidence was 50 % lower in patients with a 30 % or more reduction in urinary collagen type I cross-linked N-telopeptides (NTx) [83]; the relationship between the bone turnover response and fracture risk reduction with other agents in adults remains under study.

In children, BTM provide some insight into general diagnostic categories; for example, urinary NTx levels are high prebisphosphonate treatment in children over 3 years of age with OI [84] and correlate with an increased trabecular bone formation rate on transiliac biopsies [85]. Low BTM and trabecular bone formation are frequently observed in chronic illness osteoporosis both before [39, 86] and after years [39] of GC therapy. *LRP5* mutations causing juvenile osteoporosis are also characterized by low BTM and trabecular bone formation [87, 88]. On the other hand, brisk increases in BTM can signal recovery from growth failure and bone mass deficits as observed in children undergoing effective treatment for Crohn's disease [15]. A low alkaline phosphatase can separate patients with OI from those with hypophosphatasia—an important distinction since bisphosphonates are contraindicated in hypophosphatasia, and furthermore, a life-saving medical therapy is now available to treat the severe infantile form [89].

BTM have been measured in children undergoing osteoporosis treatment. Urinary NTx levels were suppressed during intravenous (IV) bisphosphonate therapy for OI [39, 84], including in a controlled trial [90], and remained low up to 2 years following treatment discontinuation [84]. The effect of oral bisphosphonate therapy on resorption markers has been inconsistent, with no effect in one controlled study [91] and suppression in others [92, 93]. To date, there are no studies in childhood which have assessed the fracture risk reduction or frequency of adverse effects according to thresholds of bone turnover reduction with bisphosphonate therapy. At the present time, BTM during pediatric osteoporosis therapy serve to document that the drug is exerting the anticipated biological effect and provide an index of compliance.

The definition and diagnosis of osteoporosis in children

The definition and diagnosis of osteoporosis in children has been fraught with challenges and controversy over the years, following the widespread availability of BMD by DXA that led to zealous testing in myriad pediatric populations. The initial approach in the 1990s was to adapt the adult strategy at the time and thereby diagnose a child with osteoporosis

based on a BMD Z-score ≤−2 SD. This led to an outcry of publications which highlighted the underestimation of BMD Z-scores in some because of permanent or transient short stature and/or delayed skeletal maturation relative to age- and gender-matched peers, along with recommendations for various size-correction methods in order to prevent inappropriate diagnoses of osteoporosis in short or skeletally delayed children [68, 69, 94, 95]. Subsequently, concern was raised that in the absence of large, natural history studies to understand the fracture risk associated with a given BMD Z-score, a BMD-only definition of osteoporosis in children still ran the risk of overdiagnosis even with BMD size correction. This line of thinking culminated in the ISCD convening a task force in 2007 which recommended that the definition of osteoporosis be reserved for children with both a clinically significant fracture history and a BMD Z-score ≤−2 SD [96]. This approach was viewed as a positive step forward by the pediatric bone health community, as it placed the evaluation of bone fragility in equipoise with DXA-based BMD assessments. However, the unresolved fact remained that children could have clinically significant fractures despite BMD Z-score parameters *above* the proposed, critical Z-score threshold of −2 SD [39, 49]. With these observations, concern was raised that the pendulum had swung the other way and that the 2007 ISCD criteria might lead to an appropriate diagnosis of osteoporosis being withheld from a child with overt bone fragility in the presence of a statistically "normal" BMD Z-score.

Around the same time, the clinical relevance of BMD testing was affirmed by numerous studies showing a clear, inverse relationship between BMD Z-scores and low-trauma fractures in children (Table 3). However, the proportion of children assigned a BMD Z-score ≤−2.0 varied considerably depending on the BMD normative database that was used to generate the Z-scores [47–49], once again calling into question the utility of a BMD Z-score threshold as part of the definition of osteoporosis in children. To explore the issue further, the Canadian STOPP Consortium reported the magnitude of the disparity in LS BMD Z-scores generated by normative databases from both Hologic and Lunar machines in children with ALL at diagnosis [49], highlighting a difference as much as 2.0 SD depending upon which database was used to generate the Z-scores. Secondly, this study showed that 48 % of children with VF at the time of leukemia diagnosis had BMD Z-scores >−2.0.

These disparate results in BMD Z-scores depending on the reference data that is used plus the fact that VF can occur above the −2 threshold suggested that the use of a LS BMD Z-score cut-off as part of the definition of osteoporosis in children with VF was not valid [49]. This view has been underscored by the ISCD in an updated (2013) position statement [29] which notes that a BMD Z-score threshold of ≤−2.0 is no longer required to diagnose osteoporosis in a child with a VF; in fact, there are no longer BMD Z-score requirements at all in the setting of a low-trauma VF. In the 2013 ISCD recommendation, the use of a BMD Z-score threshold (−2.0 or worse) has been retained to denote osteoporosis in children with long bone fractures, provided such children also have a clinically significant fracture history defined as ≥2 long bone fractures by age 10 and ≥3 long bone fractures by age 18 [29]. At the same time, the 2013 ISCD position statement notes that a BMD (or bone mineral content) Z-score >−2.0 does not preclude an increased fracture risk of long bone fractures. This caveat is affirmed by the report of Henderson et al. that up to about 15 % of children with neuromuscular disorders and lower limb fractures had lateral distal femur BMD Z-scores >−2.0 [37].

Despite the disparity in LS BMD Z-score generated by different normative databases, Ma et al. [49] showed in children with ALL at diagnosis that the relationships between LS BMD Z-scores and VF are consistent regardless of the reference databases that are used to generate the Z-scores. This is not surprising, since the available reference databases are all highly correlated with one another (with r value ranges from 0.85 to 0.99) [49]. These findings suggest that while the use of a LS BMD Z-score threshold is not valid for the diagnosis of osteoporosis in children with VF and that this is likely also true in relation to other BMD sites in children with extremity fractures [37], the use of LS BMD Z-scores as a continuous variable risk factor for VF in clinical research studies nevertheless remains valid.

Where does this leave the clinician in the pivotal decision to label a child with osteoporosis? On balance, current evidence puts the weight of the diagnosis on the fracture history. Among children with risk factors for osteoporosis, a low-trauma fracture is usually apparent (falling from a wheelchair, sustaining a fracture during a seizure); in such cases, a size-corrected BMD Z-score >−2.0 should not deter the clinician from the osteoporosis diagnostic label.

On the other hand, in the case of an otherwise healthy child with recurrent fractures but absence of risk factors, stigmata of OI, or a genetically confirmed family history of osteoporosis, it is incumbent upon the clinician to find evidence of additional features to support the diagnosis of osteoporosis (Fig. 1). VF without a history of trauma are highly suggestive of an underlying bone fragility condition, and the lower the BMD, the more likely an osteoporotic phenotype (although a normal BMD does not categorically rule out osteoporosis as discussed). Genetic testing is indicated in such children, since even children with type I collagen mutations can lack typical stigmata. Overall, about 7 % of patients with a mutation in the type I collagen genes will be without either blue sclerae or dentinogenesis imperfecta (Frank Rauch, personal communication).

Since over a dozen genes have now been implicated in OI or "OI-like" bone fragility (Table 1), questions have been raised about the best way to describe the various forms of

mild, moderate, and severe genetic forms of osteoporosis. While some reports retain the original OI subtype nomenclature [97] (i.e., types I to XVI, expanding on the initial classification proposed by Sillence and Rimoin [98]), recently, it has been proposed that congenital bone fragility should be described according to the implicated gene and that the term OI should be reserved for genetic forms which involve type I collagen pathobiology [99]. This approaches simplifies the diagnosis of genetic bone fragility for the clinician, clustering diagnoses into broad categories based on known genetic underpinnings (see Table 1 for phenotypic characteristics associated with each). Figure 1 provides an overview of the approach to the diagnosis of osteoporosis in children. It should be remembered that a young child with unexplained fractures, lack of evidence for a secondary cause of osteoporosis, and normal genetic studies may be the victim of nonaccidental trauma.

Treatment

General measures for optimization of bone health

First-line measures to optimize bone health fall into three main categories: nutrition, physical activity, and treatment of the underlying condition and associated comorbidities; these have also been recently reviewed elsewhere [1, 2, 100–106]. The most well-described nutritional factors for bone health are vitamin D and calcium; however, a number of other nutrients also play a role in bone metabolism, including protein, potassium, magnesium, copper, iron, fluoride, zinc, and vitamins A, C, and K. Children with chronic illnesses are at particular risk for vitamin D deficiency due to limited sun exposure, malabsorption, and dietary restrictions. Youth with eating disorders (such as anorexia nervosa) or malabsorption (short gut syndromes, celiac disease, Crohn's and exocrine pancreatic disorders) can present with extensive nutritional compromise including lack of essential dietary proteins, fats, fat-soluble vitamins, and mineral ions requiring the expertise of dieticians and gastroenterologists specializing in the underlying disease and childhood nutrition [107]. Secular trends in dietary habits also appear to have an adverse effect on bone health, with high intake of sugar-sweetened drinks associated with an increased fracture risk [105].

The recommended intake of vitamin D is a minimum of 600 IU/day [107], although higher doses are often required to meet target levels, particularly in those with malabsorption, obesity, and darker skin [107]. Adequate total body vitamin D stores have been defined at a serum 25-hydroxyvitamin D level ≥50 nmol/L (20 ng/mL) [107, 108] or ≥75 nmol/L (30 ng/mL) [109], mostly based on adult studies. In children, the optimal serum 25OHD threshold remains under debate. A meta-analysis showed a lack of significant effect of vitamin D supplementation and 25OHD levels ≥50 nmol/L on BMD in healthy youth [110], a bone histomorphometric study in children with OI failed to show an association between serum 25OHD levels and bone mineralization or bone mass [111], and calcium plus vitamin D supplementation had no effect on spine BMD in children with inflammatory bowel disease [112] and leukemia [113]. Overall, the optimal serum 25OHD threshold associated with health benefits across the life cycle remains controversial as discussed in a large contemporary "umbrella" assessment of published systematic reviews and meta-analyses [114]. From a practical perspective, a minimum 25-hydroxyvitamin D level of 50 nmol/L (20 ng/mL) is recommended in youth through diet and/or supplementation, with measurement of 25-hydroxyvitamin D in high-risk populations ideally at the end of winter in order to determine compliance with and efficacy of prescribed doses at the time of the nadir.

The Institute of Medicine [107] recommends age-specific dietary reference intakes for calcium for all life stages. The recommended dietary allowance of calcium to fulfill the needs of 97.5 % of the healthy population is 700 mg/day for children 1 to 3 years, 1000 mg/day between 4 and 8 years, and 1300 mg/day for children 9 to 18 years [107]. Higher daily supplementation may be required in children with malabsorption or medications that impair calcium retention or absorption (diuretics or GC therapy). Optimizing calcium intake through diet is preferred because of questions raised following reports of adverse cardiovascular outcomes in adults following supplementation [115]. The role of routine calcium supplementation in childhood has been queried by a meta-analysis showing only a small effect on BMD unlikely to alter fracture risk [116]. On balance, calcium is a key nutrient for adequate skeletal mineralization with recommended intakes best achieved through a healthy diet.

High impact activity has an anabolic effect on the growing skeleton and has been shown to increase bone mass in healthy children, particularly those prepubertal and in early puberty [106, 117]. The impact of physical activity in children with chronic illnesses remains virtually unchartered; a pilot study in children after cancer therapy showed an increase in total body and femoral neck BMD compared to controls after 6 months of group-based aerobic and strength training exercises [118]. Modified exercise (i.e., activities with a low risk of falls and bodily contact) should be encouraged within the limits of the underlying condition in ambulatory children with osteoporosis. Among youth with more severe physical impairment, modest increases in BMD have been reported following standing regimes as well as physical and high-frequency vibration therapy [119]; the impact of such interventions on fracture risk requires further testing in larger, longer-term studies. The benefits of exercise appear maximal under conditions of adequate calcium intake [104], underscoring the importance of implementing these general measures in tandem.

For children with chronic illnesses, adequate treatment of the underlying illness is the mainstay of osteoporosis prevention and treatment. The situation is complicated by the fact that some of the standard therapies are osteotoxic, including GC, high-dose methotrexate in the cancer setting [120], calcineurin inhibitors [121], hepatic microsomal enzyme-inducing antiepileptics increasing catabolism of 25-hydroxyvitamin D, and long-term use of anticoagulants [122] and medroxyprogesterone [123]. Wherever possible, these agents should be used sparingly in children with risk factors for osteoporosis, a principle that is not always practical given, for example, the need for GC therapy to treat systemic inflammatory diseases and leukemia and to slow the progression of the myopathy in DMD. Identification of endocrine comorbidities is also appropriate, including treatment of delayed puberty, growth hormone deficiency, hyperthyroidism, and diabetes. Growth hormone therapy increases areal BMD even after final adult height attainment and should be continued through adulthood in those with low size-adjusted BMD or fractures [124]. As a word of caution in the use of growth hormone to treat GC-induced growth failure in DMD—in addition to a paucity of data to support the safety and efficacy of this approach, one of the current hypotheses is that short stature may be beneficial to muscle strength in DMD since stresses on the sarcolemma are higher with increases in the size of the muscle fiber [125].

Drug therapy: candidates for medical intervention and timing of treatment initiation

When to initiate medical treatment is a frequently posed question by clinicians. To date, intervention studies in children have largely been limited to case series and small observational or case-control studies, given the relative paucity of patients with various diseases at any one medical center and the challenges in securing funding for large, multicenter drug trials in the young. The absence of treatment trials targeting the prevention of first-ever fractures in children has led to a conservative approach overall, with therapy typically reserved for children with overt bone fragility. Among those with chronic illness osteoporosis, there is an additional consideration—not every child with symptomatic osteoporotic fractures and chronic illness requires osteoporosis therapy given the potential for spontaneous (medication-unassisted) recovery if risk factors are transient, including reshaping of previously fractured vertebral bodies. The potential for spontaneous recovery in children with transient risk factors demands controlled trials in this setting.

Where primary prevention with drug therapy prior to the first fracture is concerned, at the present time, there is insufficient data to recommend osteoporosis therapy other than the general measures discussed previously. In the future, primary prevention drug trials should target priority disease groups including the progressive neuromuscular disorders like GC-treated DMD. Here, there is an urgent need for well-designed trials on sufficient numbers of patients to effectively assess functional outcomes including fractures, pain, and mobility when treatment is started before the first fracture.

Since there are insufficient data to recommend drug therapy for the primary prevention of osteoporotic fractures in children with any condition at the present time careful monitoring in at-risk children to identify those with early signs of bone fragility, particularly in those with limited potential for spontaneous recovery, is indicated. Such an approach follows the principles of secondary prevention—to mitigate osteoporosis progression and foster recovery in those with earlier (rather than later) signs of osteoporosis. Given the knowledge that has emerged about the clinical populations at risk for osteoporosis and the disease-specific predictors of fractures, it is no longer appropriate for children to present to medical attention with, for example, back pain due to advanced vertebral collapse necessitating "rescue therapy." Rather, pediatric programs should be established to effectively monitor at-risk children in order to identify earlier stages of vertebral collapse, followed by an assessment of the child's potential for medication-unassisted recovery versus need for osteoporosis treatment. A monitoring program also provides the clinician with an opportunity to identify and treat vitamin D, mineral, and hormonal deficiencies, to encourage a healthy weight, to promote physical activity within the limits of the child's underlying condition and to encourage compliance with treatment of the underlying condition [15, 126].

Bisphosphonate therapy is typically reserved for children with a history of low-trauma fractures but also limited potential for spontaneous (i.e., medication-unassisted) recovery due to permanent or persistent osteoporosis risk factors (Fig. 1). Low-trauma long bone fractures and symptomatic VF (or asymptomatic VF that are moderate or severe) are the most frequent indications for treatment. Extremity fractures at sites other than long bones (such as the hands and feet) do not usually warrant treatment. Studies are currently underway to evaluate the safety and efficacy of treating mild (Genant grade 1) asymptomatic or minimally symptomatic VF in pediatric osteoporosis; for now, it is recommended that such fractures be closely monitored for symptomatology and/or progressive vertebral height loss that would prompt treatment.

After determining the child's vertebral and long bone fractures status, the clinician assesses the potential for medication-unassisted recovery in view of the osteoporosis severity (including degree of vertebral collapse), residual growth potential, and whether risk factors are persistent or resolving. In the face of resolving risk factors at a young age (such as withdrawal of GC therapy in a prepubertal child), a conservative approach can often be taken that involves monitoring to document the child's anticipated recovery. In contrast, children who are peripubertal or older as well as younger children with

ongoing risk factors or heritable forms of osteoporosis will have less potential for spontaneous reshaping of vertebral bodies and reclamation of BMD—such children are optimal candidates for osteoporosis therapy. Of course, symptomatic osteoporosis (such as pain from VF limiting the child's quality of life) is itself an indication for treatment; in such cases, osteoporosis therapy is recommended to relieve pain and allow the child to regain quality of life regardless of the child's potential for spontaneous recovery in the future.

Following these steps facilitates the decision to start treatment in a child with a clear diagnosis of primary or secondary osteoporosis. As shown in Fig. 1, a frequent conundrum is whether to start treatment without a specific underlying diagnosis—a scenario referred to as "low-trauma, recurrent (usually extremity) fractures in otherwise healthy children." In such cases, the clinician needs to make every effort to unearth a known cause, including the now expanded etiologies of heritable bone fragility outlined in Table 1 or chronic illnesses with insidious onset (such as Crohn's or rheumatic diseases) outlined in Table 2. A low-trauma VF in this setting is highly suggestive of a bone fragility condition. When genetic and chronic illness evaluations are negative, a transiliac bone biopsy can also provide important clues although it is less readily available. When no specific diagnosis is forthcoming despite a comprehensive evaluation, the criteria to label a child with osteoporosis provided in the most recent ISCD position statement supports the decision to initiate osteoporosis treatment: ≥2 long bone fractures by age 10 or ≥3 or more long bone fractures by age 18 *and* a size-corrected BMD or bone mineral content Z-score of −2 [29]. Low-trauma VF may also prompt treatment in these cases.

Bisphosphonate treatment of primary and secondary osteoporosis in childhood

Bisphosphonates, synthetic analogs of pyrophosphate, are the most extensively published agents to treat osteoporosis in childhood [127, 128], despite the fact that they remain off-label in most countries. The vast majority of publications describing the effect of bisphosphonate therapy in children are observational, pre-post studies; there are relatively few controlled studies of bisphosphonate therapy in children and even fewer studies have been sufficiently powered to assess fracture outcomes. The paucity of fracture outcome data in controlled trials reflects a number of considerations when studying children: the relatively small numbers of patients available for study, the historically adult focus of industry-sponsored trials, and the logistical and philosophical challenges of enrolling younger patients. The latter issue includes pressure from families and health-care providers alike to treat individual pediatric patients despite insufficient evidence, instead of enrolling children in controlled trials that address uniquely pediatric safety and efficacy issues. Nevertheless, the few controlled studies available in addition to a number of key observational studies provide important and useful information about pediatric patients' responses to bisphosphonate therapy.

Oral versus intravenous bisphosphonate therapy

The use of oral versus IV bisphosphonate therapy for pediatric osteoporosis has long been debated [129]. Overall, IV pamidronate is the mostly extensively reported agent in children following the inaugural observational study in the late 1990s which showed improved pain, mobility, and reshaping of vertebral bodies following pamidronate therapy in children with moderate to severe OI [130]. Children were treated with cyclical, IV pamidronate at a dose of 9 mg/kg/year divided every 2 to 4 months up to 5 years' duration [130]. In recent years, IV zoledronic acid has been introduced given the advantage that it can be given over a shorter period of time and less frequently [39, 131]; zoledronic acid is 100 times more potent than pamidronate [132]. Both agents are nitrogen-containing bisphosphonates that inhibit farnesyl diphosphate synthase and thereby protein prenylation, a process crucial for osteoclast survival. A randomized study comparing the two agents in OI showed that zoledronic acid had similar effects on LS BMD Z-scores and fracture rates over 12 months [131]. Of the oral agents, alendronate and risedronate have been the most extensively studied, with one report confirming that the oral bioavailability of alendronate in children is <1 %, similar to adults [133].

Figure 3 shows the mean difference in LS areal BMD Z-score change in published, controlled trials of bisphosphonate therapy for the treatment of childhood osteoporosis, with comparison of results in the treatment versus placebo/untreated control groups. As shown in Fig. 3, increases in spine BMD Z-scores were a consistent finding in all of the available controlled studies using oral alendronate or risedronate in children with OI; one report showed no effect of oral alendronate in a study of girls with anorexia nervosa (AN) (see section on Special Treatment Considerations) [134]. In addition, a controlled study by Gatti et al. in pediatric OI (Table 4) showed a significant effect of IV neridronate on the percent change in spine and hip BMD compared to controls after 1 year. Overall, it appears that IV and oral bisphosphonates consistently increase BMD parameters in children, as confirmed in recent Cochrane reviews on the use of bisphosphonates in pediatric secondary osteoporosis [128] and OI [127].

On the other hand, the effects of IV versus oral bisphosphonates on fracture outcomes are less homogeneous, an observation that is evident in Fig. 4 (describing the relative risk of fractures in controlled bisphosphonate trials from data on the number of patients with fractures in the two groups) and Fig. 5 (showing the incidence rate of fractures in controlled trials from data on the number of fracture events in each group). Of the nine studies which permitted calculation of the relative risk of non-VF, only one by Bishop et al. [135] using risedronate in

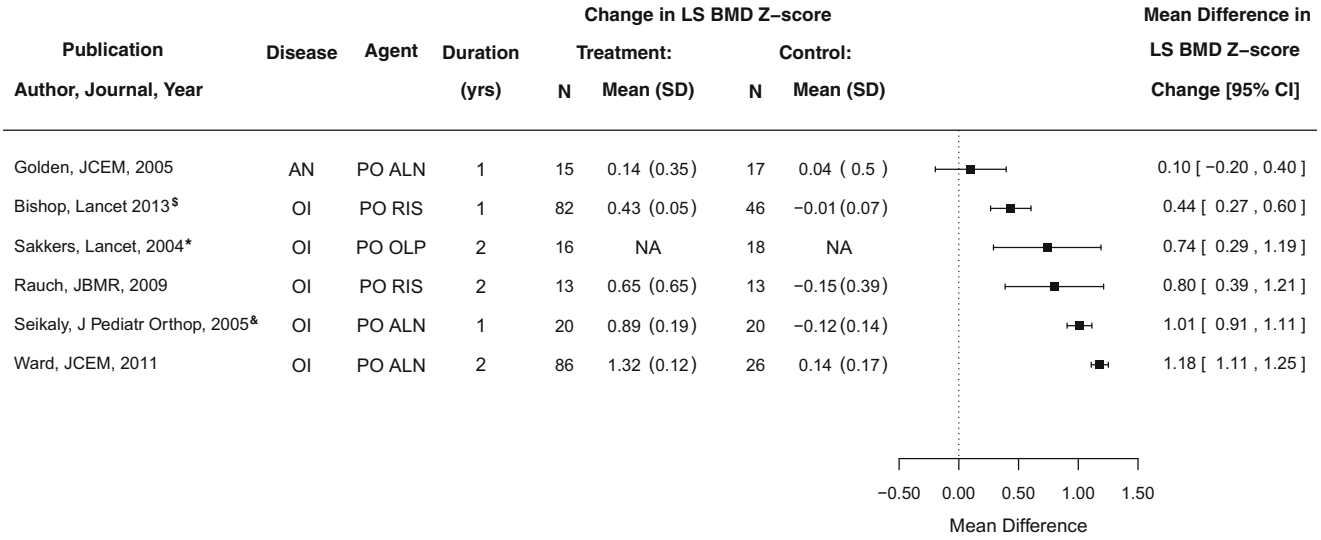


Fig. 3 Mean difference in the lumbar spine areal BMD Z-score in published, controlled trials of bisphosphonate therapy for the treatment of children with osteoporosis, with comparison of the results for the treatment versus placebo/untreated control groups. Studies were included with the following criteria: (1) at least 10 patients per group, (2) prospective design with a placebo or untreated control arm, and (3) available data on either the pre- and posttreatment change in LS BMD Z-score with standard error OR the percent change in LS BMD Z-score. *Asterisk*, Details about the magnitude of the mean change in LS BMD Z-score were not reported; however, the effect size with 95 % CI was provided. *Superscripted ampersand*, Seikaly et al. [196] was a placebo-controlled crossover study design with the results from the first year of the study presented. *Superscripted dollar sign*, Bishop et al. [135] reported least-squares mean difference. *ALN* alendronate, *AN* anorexia nervosa, *CF* cystic fibrosis, *GC* glucocorticoids, *IV* intravenous, *yrs* years, *NER* neridronate, *OI* osteogenesis imperfecta, *OLP* olpadronate, *PO* oral, *Pts* patients, *RIS* risedronate

pediatric OI showed a decrease in non-VF risk. The other studies in Fig. 4 [91, 93, 134–139] found no significant differences compared to placebo or untreated controls in the relative risks of non-VF after oral alendronate, oral olpadronate, and IV neridronate. At the same time, Fig. 4 highlights that the direction of effects for non-VF risks in the nonsignificant studies was favorable for treatment in all but one study [134]. Figure 5 shows the incidence rate ratio of fractures using the number of fracture events in the two groups (a more powerful calculation since there are typically more fracture events than patients with at least one fracture). Two studies with nonsignificant results for the relative risk of non-VF had positive results when the incidence rate ratio was calculated [91, 138]. Most of the nonsignificant estimates in Figs. 4 and 5 had extremely wide confidence intervals but directions of effect in favor of treatment, suggesting that sample sizes were likely inadequate to show differences in fracture rates between the two groups.

So how do we adjudicate whether oral or IV bisphosphonate therapy is more efficacious in the presence of such little controlled data and inadequate sample sizes to determine the effects on fractures? The answer appears to lie in the VF and vertebral body reshaping data. Based on observational studies, it is expected that fractured vertebral bodies will undergo reshaping with bisphosphonate therapy [39, 53, 140, 141], thereby providing a key index of benefit. The controlled trials to date which quantified vertebral body height clearly showed increases in those receiving IV bisphosphonate therapy [90, 138, 142], whereas none of the controlled oral bisphosphonate studies in which it was measured showed a positive effect on vertebral height [91–93]. Furthermore, in a large randomized trial of daily oral alendronate for moderate and severe pediatric OI [139], there was no effect of alendronate on the cortical width of transiliac specimens. In contrast, this is a key structural index derived from a precise measurement which has shown a positive response in OI to IV bisphosphonate therapy [85]. Another compelling observation that supports IV over oral therapy is from a controlled OI trial [93], where risedronate did not lead to an increase in the trabecular volumetric BMD at the distal radius compared to placebo; on the other hand, IV therapy caused significant increases in BMD at this site [143]. Overall, these data support the use of IV instead of oral bisphosphonate therapy first-line. At the same time, Figs. 4 and 5 underscore the need for controlled trials of osteoporosis therapies, especially in the secondary osteoporosis where there are only three controlled trials published to date and none sufficiently powered to address any fracture outcomes.

Monitoring the efficacy of bisphosphonate treatment

Gauging the efficacy of bisphosphonate therapy rests on a number of clinical parameters, most of which are focused on the functional musculoskeletal health of the child. One of the main goals of therapy is remittance of back and bone pain which typically occurs within 2 to 6 weeks following

Table 4 Bisphosphonate therapy in children: results of prospective controlled trials with at least 10 patients per group

Publication, study design, and diagnosis	Number of patients, age (years)	Agent, dose, and route	Main efficacy outcomes	Side effects
•Bishop et al. [135] •RCT, double-blind •OI (mild to severe) •Duration with comparison to control group: 1 year	Treatment group •*N* = 94 •Age: mean (SD) = 8.9 (3.4) Placebo group •*N* = 49 •Age: mean (SD) = 8.6 (3.1)	•Oral risedronate •2.5 mg/day if weight 10–30 kg; 5 mg/day if weight >30 kg	•See BMD and fracture outcomes in Figs. 3 and 4 •↓ Urinary NTx/creatinine with risedronate versus placebo	•Similar between treatment and placebo groups
•Ward et al. [139] •RCT, double-blind •OI (mild to severe) •Duration: 2 years	Treatment group •*N* = 109 •Age: mean (SD) = 11.0 (3.6) Placebo group •*N* = 30 •Age: mean (SD) = 11.1 (4.0)	•Oral alendronate •5 mg/day if weight <40 kg; 10 mg/day if weight ≥40 kg	•See BMD and fracture outcomes in Figs. 3 and 4 •↓ In urinary NTx with risedronate versus placebo •No differences: average midline vertebral height, iliac cortical width, bone pain, physical activity	•Similar between treatment and placebo groups
•Gatti et al. [138] •RCT, unblinded •OI (mild to severe) •Duration: 1 year	Treatment group •*N* = 42 •Age: mean (SD) = 9.0 (2.3) Untreated control group •*N* = 22 •Age: mean (SD) = 8.6 (2.4)	•IV neridronate •2 mg/kg every 3 months •Intravenous	•See fracture outcomes in Figs. 4 and 5 •Significant differences compared to untreated controls: •↑ spine and hip BMD •↑ height and DXA-derived LS projected area •↓ Total number of fractures •Nonsignificant differences compared to untreated controls: number of patients with nonvertebral fractures	•Flu-like symptoms; 10/42 in the neridronate group; 0/22 in the untreated control group
•Sakkers et al. [91] •RCT, double-blind •OI (mild to severe) •Duration: 2 years	Treatment group •*N* = 16 •Age: mean (SD) = 1.0 (3.1) Placebo group •*N* = 18 •Age: mean (SD) = 10.7 (3.9)	•Oral olpadronate •10 mg/m^2 daily	•See BMD and fracture outcomes in Figs. 3, 4, and 5 •Significant differences compared to placebo: •↓ Relative risk of long bone fractures •↑ spine BMC •Nonsignificant differences compared to placebo: mobility, self-care, muscle strength, anthropometry, vertebral height, urinary bone resorption markers	•Not reported
•Rauch et al. [93] •RCT, double-blind •OI type I •Duration: 2 years	Treatment group •*N* = 13 •Age: mean (SD) = 11.7 (3.6) Placebo group •*N* = 13 •Age: mean (SD) = 11.9 (4.0)	•Oral risedronate •15 mg/week if weight <40 kg; 30 mg/week if weight >40 kg	•See BMD and fracture outcomes in Figs. 3, 4, and 5 •Significant differences compared to placebo: •↓ Serum NTx •Nonsignificant differences: BMC/BMD at the radial metaphysis and diaphysis, hip, and total body; transiliac cortical width, trabecular bone volume, bone turnover; vertebral height; second metacarpal cortical width, grip strength, bone pain	•Similar between treatment and placebo groups
•Seikaly et al. [196] •RCT with double-blind crossover design •OI (mild to severe) •Duration: 1 year treatment then crossover to placebo OR 1 year placebo then crossover to treatment	Treatment group •*N* = 20 Age: mean (SD) = 9.8 (1.06) Placebo group •Crossover design, therefore same patients as in the treatment group	•Oral alendronate •5 mg/day if weight <30 kg; 10 mg/day if weight >30 kg	•See BMD and fracture outcomes in Figs. 3 and 5 •Significant differences compared to placebo: •↑ improved QOL scores, except for mobility •↑ height Z-score •↓ Urinary NTx •Nonsignificant differences compared to placebo: serum calcium, osteocalcin, PTH, 1,25(OH)$_2$ vitamin D$_3$, urinary hydroxyproline	•Alendronate group: 2/20 had mild gastrointestinal discomfort; 0/20 in the placebo group

Table 4 (continued)

Publication, study design, and diagnosis	Number of patients, age (years)	Agent, dose, and route	Main efficacy outcomes	Side effects
•Bianchi et al. [136] •RCT, double-blind •Cystic fibrosis •Duration: 1 year	Treatment group: •*N* = 65 •Age: mean (SD) = 13.5 (5.3) Placebo group: •*N* = 63 •Age: mean (SD) = 13.2 (5.1)	•Oral alendronate •5 mg/day if weight ≤25 kg or 10 mg/day if weight >25 kg	•See fracture outcomes in Figs. 4 and 5 •Significant differences compared to placebo: •↑ LS BMAD •↑ proportion of patients who attained a normal-for-age bone BMAD Z-score •↓ Serum CTx and urinary NTx •↓ Serum bone-specific alkaline phosphatase •Nonsignificant differences compared to placebo: serum osteocalcin, PTH	•Similar between treatment and placebo groups
•Golden et al. [134] •RCT, double-blind •Anorexia nervosa •Duration: 1 year	Treatment group: •*N* = 15 •Age: mean (SD) = 16.9 (1.6) Placebo group: •*N* = 17 •Age: mean (SD) = 16.9 (2.2)	•Oral alendronate •10 mg/day	•See BMD and fracture outcomes in Figs. 3 and 4 •Significant differences compared to placebo •↑ femoral neck vBMD •Nonsignificant differences compared to placebo: femoral neck and LS areal BMD, bone-specific alkaline phosphatase, urinary deoxypyridinoline	•Placebo group: 1 patient discontinued the medication because of dyspepsia •Adverse events otherwise similar between groups
•Rudge et al. [137] •RCT, double-blind •Chronic illness treated with GC therapy •Duration: 1 year	Treatment group: •*N* = 11 •Age: median (min, max) = 8.7 years (6.3, 14.5) Placebo group: •*N* = 11 •Age: median years (min, max) = 8.0 (4.3, 17.2)	•Oral alendronate •1–2 mg/kg once-weekly	•See fracture outcomes in Figs. 4 and 5 •BMD: comparisons between groups not reported •Alendronate group: ↑ LS vBMD compared to baseline •Placebo group: no change in LS vBMD compared to baseline •Nonsignificant differences compared to placebo: alkaline phosphatase	•No major adverse events in either treatment or placebo group

Studies were included with the following criteria: (1) prospective comparison of drug versus placebo or untreated controls, (2) at least 10 patients per group, and (3) outcomes were compared between, and not just within, treatment and control groups

BMC bone mineral content, *BMD* bone mineral density, *BMAD* bone mineral apparent density, *vBMD* volumetric bone mineral density, *CTx* serum C-telopeptide of type I collagen, *GC* glucocorticoid, *LS* lumbar spine, *NTx* urinary N-telopeptide of type I collagen, *OI* osteogenesis imperfecta, *PTH* parathyroid hormone

IV bisphosphate therapy [39, 130]. In a child with VF, follow-up spine radiographs should be carried out in order to evaluate a number of efficacy parameters as outlined in Fig. 1.

In addition, the history of new non-VF should be recorded, along with details about the site of fracture, degree of trauma associated with the injury, need for surgical management, impact to quality of life, and duration of healing. Improvements in energy level [130], mobility, and muscle strength [144] are also monitored. BMD parameters are tracked as a measure of efficacy following initiation of bisphosphonate therapy; however, there are no studies which have addressed which BMD increment or cut-off is associated with a clinically acceptable decrease in fracture rates posttreatment initiation. In the absence of such data, a reasonable rule of thumb is that the areal BMD Z-score should stabilize (if previously on the decline) or increase beyond the precision of the measurement and, furthermore, the areal BMD Z-score will approximate the patient's height Z-score. Another approach is to aim for a BMD Z-score >−2 SD [53].

Bisphosphonate dose adjustments, duration of treatment, and effect of treatment discontinuation

The most frequently prescribed IV bisphosphonate regimen is cyclical IV pamidronate (maximum dose 9 mg/kg/year for children ≥3 years, 3 mg/kg divided equally over 3 days given every 4 months) [5, 84, 128, 130, 145]. Due to high bone turnover in younger children, pamidronate is dosed more frequently (2.25 mg/kg divided equally over 3 days, every 3 months for children 2 to 3 years of age, and 1.5 mg/kg divided equally over 3 days, every 2 months for children <2 years of age). Zoledronic acid is increasingly used in clinical care due to its ease of less frequent dosing intervals and shorter infusion time compared to pamidronate (maximum dose 0.1 mg/kg/year given as two equal doses (0.05 mg/kg) every 6 months in children ≥2 years and 0.025 mg/kg every 3 months in children <2 years) [131, 146, 147]. Some investigators have favored a lower annual starting dose (such as a single-day pamidronate infusion 1 mg/kg every 3 months, 4 mg/kg/year) [148, 149]. Apart from these regimens,

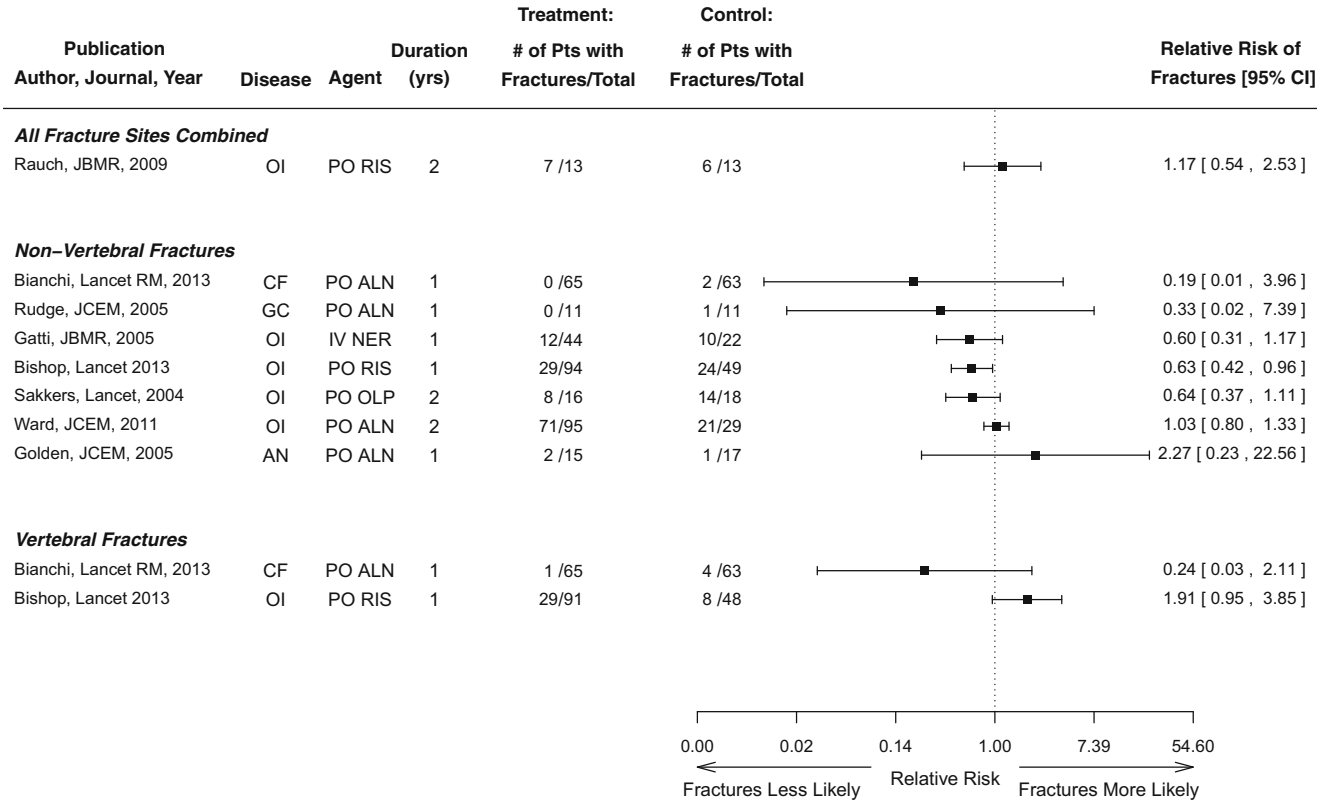


Fig. 4 Relative risk of vertebral and nonvertebral fractures in published, controlled trials of intravenous or oral bisphosphonate therapy for the treatment of children with osteoporosis, with comparison of the number of children with fractures in the treatment versus placebo/untreated groups. Studies were included in the figure if they met the following criteria: 1. At least 10 patients per group, 2. Prospective design with a placebo or untreated control arm, and 3. Available data on the number of patients with fractures in each group. *ALN* alendronate, *AN* anorexia nervosa, *CF* cystic fibrosis, *GC* glucocorticoid-treated, *IV* intravenous, *yrs* years, *NER* neridronate, *OI* osteogenesis imperfecta, *OLP* olpadronate, *PO* oral, *Pts* patients, *RIS* risedronate

other IV doses and intervals have also been reported (Table 4) though none has gone head to head in controlled, comparative trials, the exception being pamidronate versus zoledronic acid which showed similar effects on BMD and fracture rates in OI [131]. With such little controlled comparative data, it is impossible to state which IV agents and regimens achieve the best results for mitigating fractures and pain and improving overall function. Regardless, bisphosphonate therapy should only be administered by clinicians with the appropriate expertise and infrastructure to support peri-infusion care, and the maximum, published annual doses should not be exceeded so as to avoid iatrogenic osteopetrosis arising from toxic doses [150].

The approach to dose adjustments and the duration of bisphosphonate therapy are also questions frequently posed by pediatricians. A number of key observations unique to children have influenced practice in this regard. The first observation has led to continuing bisphosphonate therapy until final height attainment in those with permanent or persistent risk factors, as follows. Among children with open epiphysis and ongoing endochondral bone formation, following treatment discontinuation, the newly formed bone adjacent to the growth plate will be "treatment-naive" and thereby low density, creating a stress riser between high (previously treated) and low (untreated) density bone [143]. Not surprisingly, metaphyseal fractures have occurred postbisphosphonate discontinuation in children with OI (i.e., in children with persistent risk factors for low bone density) at the interface between the treated and untreated bone [151]. In fact, metaphyseal fractures have even occurred *during* intermittent IV bisphosphonate therapy at the interface between the dense metaphyseal lines created at the time of therapy and the (2-mm) adjacent treatment-naive bone [152]. This latter report raises the question whether IV bisphosphonates should be administered with as short an infusion interval as possible, a line of thinking that is challenged by the demands on the patient from frequent infusions.

Further support for continuation of therapy to final height in those with persistent or permanent risk factors arises from a study by Rauch et al. [151]. These investigators showed using pQCT that there were significant declines in trabecular BMC Z-scores at the distal radius following pamidronate discontinuation in children with OI who were still growing. On the other hand, discontinuation after epiphyseal fusion was associated with more stable BMD Z-scores 2 years later. Balancing these observations with the lingering concern about oversuppression with longer-term therapy, the current recommended approach is to treat patients initially with a higher dose regimen until the patient is clinically

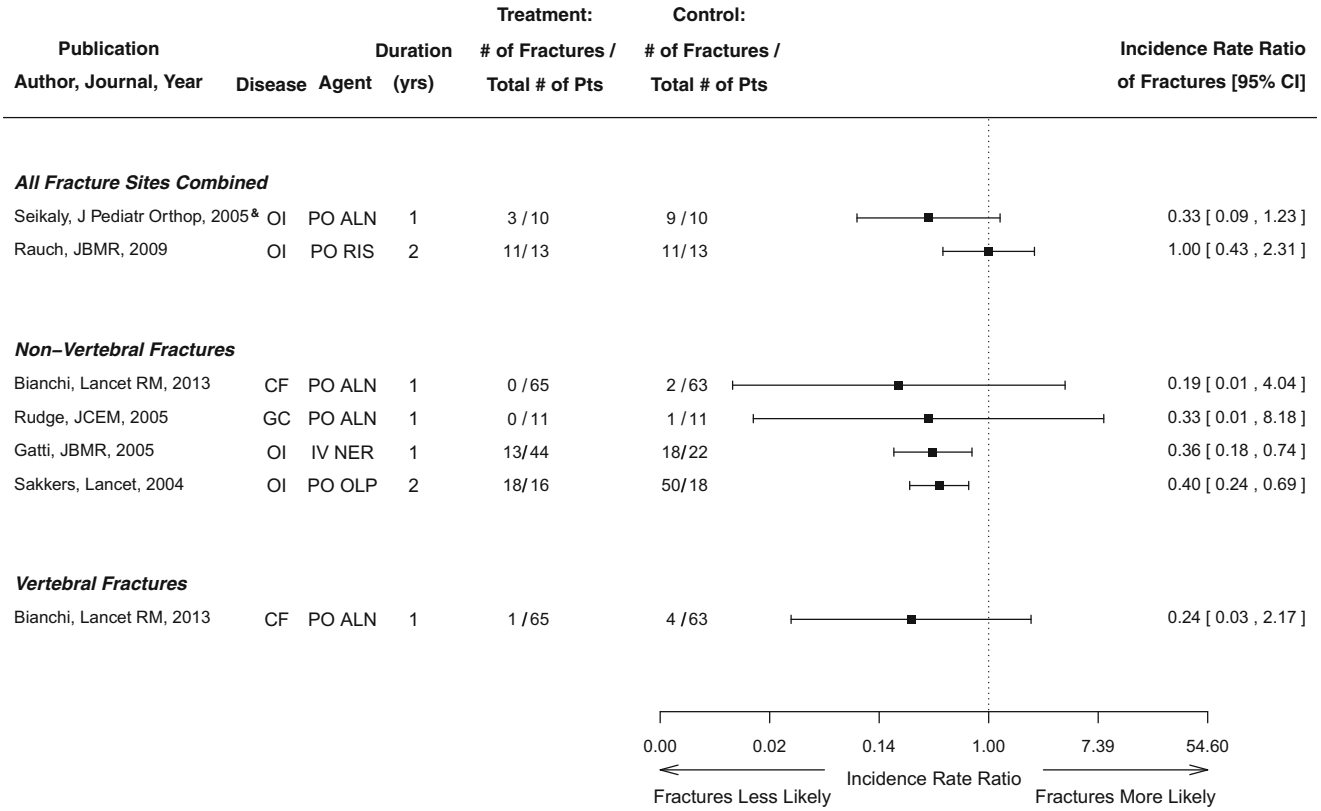


Fig. 5 The incidence rate ratio in published, controlled trials of intravenous or oral bisphosphonate therapy for the treatment of children with osteoporosis in comparison to the number of fracture events in the treatment versus placebo/untreated control groups. Studies were included with the following criteria: (1) at least 10 patients per group, (2) prospective design with a placebo or untreated control arm, and (3) data available on the number of fractures in each intervention group. *Superscripted ampersand*, Seikaly et al. [196] was a placebo-controlled crossover study design with the results from the first year of the study presented. *ALN* alendronate, *CF* cystic fibrosis, *GC* glucocorticoid-treated, *IV* intravenous, *yrs* years, *NER* neridronate, *OI* osteogenesis imperfecta, *OLP* olpadronate, *PO* oral, *Pts* patients, *RIS* risedronate

stable (Fig. 1). Usually, this equates to a minimum of 2 years, the time point at which the maximum benefit from bisphosphonate therapy has been observed in children with OI [85]. Once the patient is clinically stable, a lower (half-dose or less) [53, 153] maintenance protocol is given until the patient attains final adult height, at which time treatment can be discontinued if the patient is stable [53]. The goal of the maintenance phase of therapy in children with permanent or persistent risk factors is to preserve the gains realized during high-dose therapy while avoiding over-treatment [53, 153]. To this end, the dose of IV bisphosphonate therapy in the maintenance phase may require further downward titration to avoid unnecessarily high BMD Z-scores—this can be achieved by decreasing the dose or by increasing the interval between infusions. Palomo et al. [53] recently reported that long-term (at least 6 years) bisphosphonate therapy with downward dose titration in pediatric OI led to higher BMD Z-scores compared to historical controls and to vertebral body reshaping, although it was notable that non-VF rates were still high and most patients continued to developed scoliosis. An outstanding question about the duration of therapy in those who stop around the time of adult height attainment but have persistent risk factors for fractures (e.g., OI or ongoing GC exposure) is whether they will require reintroduction of bisphosphonate therapy in the adult years and, if so, at what time point.

In children with resolution of risk factors during growth (i.e., cessation of GC therapy, resolution of inflammation, recuperation of mobility), discontinuation of therapy can be considered once the child has been fracture-free (VF and non-VF) for at least 6 to 12 months, previously fractured vertebral bodies have stabilized or undergone reshaping, and BMD Z-scores are appropriate for height. Reintroduction of therapy may be required during growth if the prior risk factors for osteoporosis recur and patients once again meet the criteria for treatment initiation.

Use of an antiresorptive agent in low bone turnover states

While the use of an antiresorptive agent is not ideal in low bone turnover states (such as GC-induced osteoporosis or immobilization disorders), it is important to recognize that withholding bisphosphonate therapy from children with low bone turnover will prevent positive, growth-mediated skeletal effects arising from the unique synergy between antiresorptives and bone modeling. For example, at the level of the vertebral body growth plate, bisphosphonates do not interfere with endochondral bone

formation (the bone modeling process by which bones increase in length); furthermore, endochondral bone formation is independent of bone turnover on trabecular surfaces. This means that fractured vertebral bodies will reshape by endochondral bone formation despite low trabecular bone turnover provided a child is growing (with bisphosphonates having a permissive effect on reshaping by optimizing BMD). This principle has been nicely demonstrated in pediatric DMD by bone histomorphometry and serial spine radiographs [39]. Similarly, periosteal apposition is the growth-dependent process by which bones increase in width; antiresorptive therapy leads to bone catabolism on endocortical surfaces but periosteal apposition proceeds normally. This brings about a net increase in cortical width during bisphosphonate treatment, a phenomenon first demonstrated by Rauch et al. in pediatric OI [85] and later by our group in boys with DMD [39]. At the same time, the door is decidedly open to novel anabolic therapies which would be ideal in children with low bone turnover states, a need for prolonged osteoporosis therapy and poor linear growth. The classic clinical examples of this scenario are children with systemic juvenile idiopathic arthritis and DMD. While parathyroid hormone (PTH) holds a Food and Drug Administration black box warning that prevents its use in children, the role of PTH in conditions such as this postepiphyseal fusion merits further study.

Bisphosphonate therapy side effects and contraindications

Short-term

The most frequent side effects of bisphosphonate therapy, reported with both oral and IV treatment [130, 133, 138], are collectively referred to as "the acute phase reaction" and include fever, malaise, back and bone pain, nausea, and vomiting. These symptoms usually begin 24 to 72 h following the initial dose, remit over a few days, typically do not occur with subsequent infusions or oral doses, and are effectively managed with anti inflammatory and antiemetic medications. Asymptomatic hypocalcemia is frequent even with repeat infusions (though most marked with the first), reaching a nadir usually 1–3 days postinfusion [84]. The frequency of first-dose hypocalcemia appears to be mitigated by reducing the initial dose [140], a practice that is now in widespread use. Interestingly, a lower dose with the first infusion does not appear to mitigate the frequency of acute phase side effects [140]. Symptoms have been reported in up to 30 % of children with first-infusion hypocalcemia [39, 140]. This has led to the widespread practice of prescribing calcium supplementation at published doses [107] for 5 to 10 days following the first bisphosphonate infusion, as well as ensuring vitamin D adequacy pre- and posttreatment. Children at risk for either hypocalcemia or its consequences (i.e., children with hypoparathyroidism or seizure disorders) may require even more aggressive hypocalcemia prevention such as an active form of vitamin D. Untreated hypocalcemia, hypophosphatemia, vitamin D deficiency, and rickets/osteomalacia are contraindications to bisphosphonate therapy. In these cases, the underlying vitamin D and/or mineral ion deficiency must be adequately treated before bisphosphonate therapy is administered (i.e., 25-hydroxyvitamin D level ≥50 nmol/L (20 ng/mL) and calcium intake sufficient for age).

The more serious acute side effects associated with bisphosphonate therapy in adults (such as uveitis, thrombocytopenia, and mucosal ulcerations with oral agents) are rare in children. Furthermore, a recent review of bisphosphonates in adults concluded that there is no link between bisphosphonates and atrial fibrillation, while the association between oral agents and esophageal cancer remains inconclusive [154]. In any patient with poor renal function (estimated glomerular filtration rate <35 mL/min), bisphosphonates are contraindicated. Recently, the United States Food and Drug Administration updated the label for zoledronic acid, stating that it is also contraindicated in patients with acute renal impairment and that patients should be screened for renal insufficiency prior to initiating treatment. To this end, it should be noted that serum creatinine may not be a reliable marker of renal function in those with myopathies such as DMD, raising the need for other measures such as cystatin C to ensure adequate renal function prior to each zoledronic acid infusion. In our center, we also verify normal renal function prior to all pamidronate infusions.

Long-term

Concerns about the effects of bisphosphonates on linear growth have ultimately been quelled by studies which confirm expected growth rates in children with bisphosphonate-treated OI [145] and osteoporosis [155]; there are even reports of improved growth with long-term bisphosphonate therapy [53], likely attributable to a positive effect on vertebral height. On the other hand, chronic bone turnover suppression has two rare but serious sequelae in adults: osteonecrosis of the jaw (ONJ) and atypical subtrochanteric or metaphyseal "fatigue" fractures (AFF). Both are proposed to arise from accumulated microdamage due to suppressed osteoclast activity. ONJ is defined as exposed bone in the maxillofacial area that does not heal within 8 weeks following identification by a health-care provider, in the absence of radiation therapy [156]. In children, there are no reports of ONJ despite three studies which examined over 350 bisphosphonate-treated children with OI following dental procedures [157–159]. Despite the lack of reported ONJ in children to date, one position statement has nevertheless recommended to safeguard the bisphosphonate-treated child's oral health by referral to a dentist prior to bisphosphonate initiation, completion of necessary invasive dental procedures prior to treatment initiation, regular dental evaluations by a dentist during treatment, and good daily oral hygiene [160].

AFF are also rare in adults, and while there is no direct causal link between bisphosphonates and AFF, the number of case

series and cohort analyses suggesting an association is increasing, as summarized in a recent report [154]. These fractures are located in the subtrochanteric region or femoral shaft, arise from minimal or no trauma, and are characterized by transverse or short oblique fracture lines without comminution and a medial spike when the fracture is complete [161]. They are often bilateral (in up to two thirds of cases) and may be associated with prodromal thigh pain. In the pediatric setting, Hegazy et al. [162] reported unusual femur stress fractures in children with OI and intramedullary rods on long-term bisphosphonate therapy (6 to 11 years); two patients had a "drug holiday" of 18 to 24 months prior to the femoral fractures. Of 72 children on IV pamidronate therapy, 18 had femur fractures, and of these, 6/72 met the adult criteria for AFF (8 %). All children had intramedullary rodding, none of the fractures were displaced, and all were treated successfully with protected weight-bearing and a hiatus from bisphosphonate therapy. While the duration of bisphosphonate therapy in those with AFF was reported in this study [162], there was no record of the frequency of such fractures in bisphosphonate-naive children nor the approach to pamidronate dosing (starting dose, maximum dose, dose titration, and total cumulative pamidronate dose). As such, it is difficult to know whether these results are generalizable to other centers; nevertheless, the observation is a call for concern and underscores the need for clinicians to report similar observations. Whether downward dose titration with long-term therapy such as currently practiced can obviate AFF remains unknown. Similarly, the benefits and risks of drug holidays in children with permanent or persistent bone heath threats needing long-term therapy remain unexplored. Although rare, AFF have led adult care providers to consider drug holidays in those with a low risk of first-ever fractures and in those with a moderate risk who are clinically well after 3 to 5 years of therapy [154]. High-risk adult patients, those with a history of bone fragility or a T score ≤ -2 SD, are not considered candidates for drug holidays [154].

Delayed osteotomy but not fracture healing has been shown in children with bisphosphonate-treated OI and intramedullary rods; higher mobility scores were the only positive predictor of delayed healing that was identified [163]. This observation has led to withholding bisphosphonate therapy in the week leading up to surgery and withholding therapy following intramedullary rodding until adequate fracture healing has been documented on X-ray, usually about 4 months. Surgical management has also switched to the use of an osteotome instead of a power saw. With these changes to medical and surgical management, a recent study has reported a significant reduction in the frequency of delayed osteotomy healing [164].

Since the skeleton acts as an endogenous reservoir of bisphosphonates that theoretically can be mobilized in subsequent years, concern has been raised about the safety of preconceptual use. Despite this theoretical concern, there have been no human reports to date of a significant adverse effect of bisphosphonates when administered either preconception or during pregnancy. This appears to stem from the fact that the amount of bisphosphonate mobilized from the skeleton in subsequent years is clinically insignificant. For example, data from Papapoulos and Cremers [165] shows that 4 to 10 years after daily oral pamidronate administration to children with osteoporosis, a maximum of 0.13 mg/kg/year is excreted in the urine (less than 0.02 % of the annual dose). The fact that the amount released from the skeleton is clinically insignificant is supported by numerous human reports. Reviews of women or girls who have received bisphosphonates preconception or during pregnancy reported an absence of skeletal abnormalities or congenital malformations in the infants apart from marginal decreases in gestational age, weight, and transient, asymptomatic hypocalcemia [166–169]. While these data are reassuring, clinicians should ensure that menstruating females have negative pregnancy tests prior to each infusion and/or they are using a medically approved form of contraception if sexually active.

Treatment considerations in specific conditions

A detailed review of all the osteoporosis treatment considerations related to specific, underlying diseases is beyond the scope of this review. While the treatment principles outlined in this overview are broadly applicable, three scenarios which deserve special mention are OI, AN, and systemic illnesses.

Osteogenesis imperfecta

In OI and potentially other genetic forms of bone fragility, where the degree of bone fragility can be so profound so as to cause in utero fractures or fractures in infancy and early childhood, medical therapy alone may be insufficient to restore normal mobility. In such cases, intramedullary rodding is necessary to straighten lower (and sometimes upper) limb deformities, prevent fractures, and foster mobility, in combination with bisphosphonate treatment plus physio- and occupational therapy. In severe cases, bisphosphonate therapy is often required before surgical rodding can be carried out, so that there is sufficient bone to permit effective hardware insertion. As well, teeth and craniofacial abnormalities (including dentinogenesis imperfecta, basilar invagination, and jaw abnormalities) require the input of specialized dentists and surgeons such that overall, a multidisciplinary team is required to care for the child with OI, particularly in the moderate and severe forms.

Anorexia nervosa

In this condition of severe low weight, the historical occurrence of non-VF fractures has been reported at 31 % in girls compared to 19 % in healthy controls [170], while the prevalence of VF is low 2.5 % [171]. It has long been established that the best strategy to improve bone density is to gain weight and restore normal

menstrual function [172]. Oral estrogen-progesterone combinations are not effective in adults or adolescents with AN, and transdermal testosterone replacement is ineffective in adult women. Physiological estrogen replacement as transdermal estradiol with cyclic progesterone does increase bone mineral accrual in teens with anorexia, approaching that of normal weight controls. The American College of Sports Medicine has recommended that oral contraceptives be considered in amenorrheic athletics over 16 years of age, but only if BMD is declining despite sufficient weight gain [173]. A study of risedronate increased spine and hip BMD in adult women with AN; however, a controlled study of oral alendronate in teens showed no effect on LS and hip BMD compared to placebo [134]. To date, there have been no controlled trials assessing the effect of IV bisphosphonate therapy on the incidence of vertebral and non-VF, on vertebral body reshaping following prevalent VF, or on BMD in adolescent AN. Given the synergistic effects of bisphosphonates and linear growth, such a trial is warranted in young patients with AN who are still growing.

Systemic illnesses

The most pressing need for intervention trials is in the secondary osteoporosis, particularly systemic illnesses including DMD and rheumatic disorders, cerebral palsy, leukemia, and other cancers. Table 3 highlights that the prevalences and incidences of fractures in children with myriad chronic illnesses are clinically significant. Furthermore, numerous risk factors have been elucidated which allow researchers to identify which children are most appropriate for primary and secondary prevention trials. Since risk factors are often transient in the secondary osteoporosis (e.g., GC therapy, the leukemic process, inflammation), controlled trials are particularly warranted. On the other hand, children with secondary osteoporosis are the most challenging to study given the small numbers of patients at any one center, the acuity of some of these illnesses (such as cancer and systemic inflammation), and the burden of multiorgan underlying disease and comorbidities.

To date, there have only been two prospective trials comparing bisphosphonate therapy to placebo or untreated controls (with at least 10 patient per group) in this context (Table 4). Using daily oral alendronate, Bianchi et al. [136] targeted youth with cystic fibrosis and found significant increases in LS BMAD and declines in BTM compared to placebo; however, the small sample size limited the ability to assess fracture outcomes. Similarly, Rudge et al. [137] studied weekly oral alendronate in children with a variety of GC-treated illnesses; once again, small sample sizes precluded assessment of fracture outcomes. An increase in vBMD compared to baseline was noted in the alendronate group but not in the placebo group. Recent reviews [1, 2, 174–176] have unanimously agreed that the effect of bisphosphonate therapy on LS BMD and bone pain in children with conditions such as cerebral palsy, GC-treated rheumatic disorders, and DMD is consistent and favorable enough to advocate for well-designed randomized controlled trials targeting those at greatest risk for fractures. Whether the challenges of studying small numbers of sick or chronically disabled children can be overcome remains to be determined.

Novel therapies

A number of important signaling pathways that modulate bone mass have led to novel drug developments in recent years. RANKL is an essential mediator of osteoclast formation, function, and survival [177], and both preclinical and clinical data suggest that inhibition of RANKL is a viable strategy for the treatment of osteoporosis [178]. Denosumab is a human, monoclonal antibody administered subcutaneously that targets RANKL to prevent the activation of RANK, thus inhibiting bone resorption and increasing bone strength at both trabecular and cortical sites without directly interacting with bone surfaces [179]. A large study on close to 8000 women with postmenopausal osteoporosis (the FREEDOM trial) showed that denosumab 60 mg every 6 months reduced vertebral, nonvertebral, and hip fracture risk without an increased risk of side effects compared to placebo [180]. Given its convenient route of administration, favorable safety profile and proven efficacy in adults, denosumab now merits exploration in children. To date, its use on compassionate grounds has been reported in a few children with osteoporosis due to OI (type VI, a subtype which is not as responsive to IV bisphosphonate therapy as other OI forms) [181] and in children with giant cell tumors [182], aneurysmal bone cysts [183], and fibrous dysplasia [184]. Importantly, there is no evidence to date of an adverse effect of denosumab on human growth plate activity [185].

Sclerostin, the product of the *SOST* gene, binds to LRP5/6 receptors and is a powerful inhibitor of the canonical Wnt signaling pathway that results in decreased bone formation. In a mouse model of moderate-severe OI, antisclerostin antibody resulted in improved bone mass and reduced long bone fragility [73]; emerging studies in humans show similar promise [186, 187]. Not surprisingly, sclerostin levels are elevated in patients with bone loss due to immobilization disorders, a clinical setting that may benefit from sclerostin suppression. Another novel agent, odanacatib, is a potent and selective inhibitor of cathepsin K (CatK) which suppresses CatK-mediated bone resorption, but it does not suppress bone formation to the same extent as bisphosphonate therapy [188]. This oral agent is interesting in the chronic illness osteoporosis and GC-induced bone fragility settings where bone turnover is typically low [39, 86]. Finally, excessive transforming growth factor-β (TGF-β) signaling has been implicated in the pathogenesis of both *CRTAP* recessive and type I collagen dominant OI; anti-TGF-antibody rescues the phenotype in both forms of the disease, garnering interest in other high bone turnover osteoporotic states.

Future directions

There have been significant advances in the pediatric osteoporosis field over the past decade following identification of numerous heritable bone fragility genes, including those associated with phenotypes that lack the classic features of OI. In children with chronic illness, we now better understand the frequency of fractures and time points at which they are most likely to occur, as well as clinical predictors of fractures and potential for spontaneous recovery. This knowledge has facilitated the development of logical osteoporosis monitoring strategies in children with chronic illnesses and improved our understanding about the best candidates for osteoporosis therapy. Advances in our understanding of the pathobiology of osteoporosis have led to recently discovered novel drug therapies which hold promise for children with both high and low bone turnover states; their efficacies and safety now merit testing in well-designed trials. As pediatric researchers go forward, there is a need for greater consensus on the methods and clinical outcomes for reporting treatment trials so that data across studies can be better aggregated in order to draw overall conclusions. Importantly, children are not small adults and this is particularly true in the study of skeletal disorders, where bone growth and modeling distinguish the pediatric skeleton from that of the more staid adult situation. A classic example is that vertebral bodies can undergo medication assisted *and* unassisted reshaping following fractures; at the same time, declines in BMD can be profound when treatment is stopped while the child is still growing. As well, pediatricians, funding agencies, and policy makers need to consider the challenges to clinical care that are created by the lack of controlled clinical trials that address these issues [189]. Overall, optimal bone strength across the lifespan rests on outcomes which take place during the time when the skeleton is under construction—the growing years. This reminds us that it is incumbent upon the pediatric bone health communities to champion the diagnosis, treatment, and study of osteoporosis in childhood.

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Compliance with ethical standards

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