Consensus guidelines on the use of bisphosphonate therapy in children and adolescents

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Young person with Primary Osteoporosis (eg. Osteogenesis Imperfecta) with significant evidence of fragility (i.e. vertebral compression fractures OR 2 low trauma long bone fractures)

NO

YES

BISPHOSPHONATE
THERAPY NOT
INDICATED

Optimize bone
health (see text)

Consider bisphosphonate therapy:

Zoledronic acid 0.1mg/kg/year, 2 divided doses (max 5mg annually) OR
Pamidronate 9mg/kg/year, 4-6 divided doses (max 60mg/dose)

Annual review: Reassess puberty/other factors(see text); Repeat DXA

Height adjusted z score:

>0

>-2.0 but <0

<-2.0

Consider ceasing
or reduce therapy
to maintenance

Consider halving
annual dose

Continue at
same dose

Maintenance therapy: Zoledronate 0.025mg/kg annually OR
Pamidronate max. 3mg/kg/year in 2 divided doses

Cease maintenance therapy at cessation of linear growth

Secondary Osteoporosis: Low BMD z score with 2 or more low trauma long bone fractures AND/OR vertebral crush fracture irrespective of BMD

BISPHOSPHONATE
THERAPY NOT
INDICATED

NO

Optimize bone
health (see text)

YES

If appropriate, consider
pubertal induction

Treat underlying
disease/reduce (where
possible) osteotoxic
medication

Consider bisphosphonate therapy for 12 months:

Zoledronic acid 0.1mg/kg/year, 2 divided doses (max 5mg annually)
OR Pamidronate 9mg/kg/year, 4-6 divided doses (max 60mg/dose)

After 12 months bisphosphonate therapy:

Review, reassess puberty/other factors (see text); Repeat DXA

If ongoing primary issue (inflammation, glucocorticoid use, CP) or if other clinical features; such as ongoing bone pain, fragility fractures, low BMD z score, consider further 12 months treatment.

After 2 years: Review, reassess puberty/other factors; repeat DXA.
Consider ceasing treatment, or moving to maintenance phase.

No
ongoing
issues

Cease bisphosphonate
therapy

Maintenance therapy:

Zoledronate 0.025mg/kg annually OR
Pamidronate max. 3mg/kg/year in 2 divided doses

Cease maintenance therapy at cessation of linear growth

NB. If risk factors for low BMD persist (e.g., persistent chronic illness, ongoing glucocorticoid therapy) consider biannual DXA scan with possibility for top up dose of bisphosphonate if BMD is falling

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Abstract

Bisphosphonate therapy is the mainstay of pharmacological intervention in young people with skeletal fragility. The evidence for its use in a variety of conditions remains limited despite over three decades of clinical experience. On behalf of the Australasian Paediatric Endocrine Group, this evidence-based consensus guideline presents recommendations and discusses the graded evidence (using the GRADE system) for these recommendations. Primary bone fragility disorders such as osteogenesis imperfecta are considered separately to osteoporosis secondary to other clinical conditions (such as cerebral palsy, Duchenne muscular dystrophy). The use of bisphosphonates in non-fragility conditions such as fibrous dysplasia, avascular necrosis, bone cysts and hypercalcemia is also discussed. While these guidelines provide an evidence-based approach where possible, further research is required in all clinical applications in order to strengthen the recommendations made.

Introduction

Bone health is an important but often under-appreciated issue in childhood. Altogether, primary and secondary paediatric bone fragility disorders are relatively common, cause significant morbidity, and have the potential to reduce long-term bone strength (2). Unlike the vast majority of adult osteoporotic disorders, which result from bone loss in later life, paediatric osteoporosis results from a failure of normal bone development. The greatest contributors to optimal bone mass accrual and development are genetic factors, and there has been a rapid expansion in the understanding of genetic forms of skeletal fragility over recent decades (2).

The growing skeleton changes size and shape, with cortical accrual and trabecular bone development (bone modeling) that is maximal at the time of puberty. Understanding these changes is essential to assessment of paediatric bone health and to choosing an appropriate management strategy.

Paediatric secondary osteoporosis, where bone fragility is associated with an underlying medical disorder or its treatment, often has multiple factors contributing to reduced bone strength, including immobility with reduced muscle pull and reduced mechanical loading on bone, poor growth, pubertal delay, elevated cytokines, nutritional deficiency, inadequate daily calcium intake, vitamin D deficiency, and use of osteotoxic medications. Each of these needs to be considered in turn and managed to optimize outcomes.

It is recognised that recurrent long-bone fractures can occur with normal BMD (3). Consensus guidelines state that a diagnosis of osteoporosis in children requires dual energy x-ray absorptiometry (DXA) bone mineral density (BMD) Z score lower than -2 (using age, gender and height matched norms on DXA measure), as well as the presence of recurrent long bone fractures (3). In addition, a diagnosis of paediatric osteoporosis can be made in the presence of vertebral compression fracture alone, independent of a DXA measurement,

because outside of severe trauma, all vertebral compression fractures in children are considered pathological (3).

Pharmacologic treatment of paediatric osteoporosis has largely been confined to bisphosphonate therapy. Despite widespread use of bisphosphonate therapy for over three decades, significant controversy remains regarding their use in children(4).

This is a consensus guideline for use of bisphosphonates in children and adolescents, drawn from current evidence and clinical practice, with reference to published literature on the subject. The GRADE system of assessing evidence and making recommendations is utilized (5). Recommendations are listed as 1 (strong recommendation) or 2 (weak recommendation) – evidence for that recommendation is graded as per Table 1.

What are bisphosphonates?

Bisphosphonates are pyrophosphate derived medications that inhibit osteoclastic function. This guideline predominantly discusses nitrogen containing bisphosphonates, whose mechanism of action is due to disruption of the mevalonate pathway involved primarily in osteoclastogenesis. Histomorphometric studies in children show that bisphosphonates significantly reduce bone remodeling(6). They do not however reduce bone growth, trabecular bone formation or periosteal bone formation (modeling), with increases in both trabecular number (metaphyseal bone) and cortical width. Reduced bone resorption and ongoing bone growth and modeling results in the significant increase in bone mass and strength observed when bisphosphonates are administered to the growing child. Bisphosphonates are retained in the skeleton, with evidence of renal excretion 8 years after cessation of a nitrogen containing bisphosphonate, pamidronate, in young people (7).

Some inflammatory or neoplastic conditions involving bone, such as chronic recurrent multifocal osteomyelitis, or bone cysts, may also be modified by the use of these agents, with the mechanism for these effects still unclear.

Recommendations for the use of bisphosphonates in children

(1) Primary bone fragility disorders

(1) (a) Osteogenesis imperfecta (OI)

Recommendation: Intravenous bisphosphonates should be considered for use in children with severe OI (e.g. type III), children with vertebral compression fractures or children who have had two or more long-bone fractures per year. Oral bisphosphonates should only be considered for those with mild-moderate OI in the absence of vertebral compression fractures (1,⊕⊕⊕⊕O).

As outlined below, we would not recommend that children with severe OI should cease therapy once BMD improves, rather they should continue on a long-term lower dose of bisphosphonate to preserve bone strength during growth.

The annual dose of intravenous bisphosphonate can be halved once the height adjusted BMD z-score falls within the range -2 to 0.

Once BMD z-score >0, the dose can be reduced further and treatment continued at this lower dose until the cessation of growth.

In children with less severe OI it may be possible to stop bisphosphonate therapy during childhood without deterioration in clinical status or BMD.

Once a child with OI stops growing, it is recommended to suspend therapy and monitor (1,⊕O00).

Evidence:

Osteogenesis imperfecta (OI) is a heterogeneous group of bone fragility disorders characterized by low bone mass, recurrent fractures and chronic disability, with a broad spectrum of clinical severity. It can also be associated with other clinical features including scoliosis, blue sclerae, deafness, easy bruising, wormian bones and dentin hypoplasia (the cited reviews provide a good summary of diagnosis, classification and multidisciplinary management of OI(8) (9)).

The management of OI should involve a multidisciplinary team of medical, surgical and allied health-care professionals at specialized centres experienced in managing such patients. Bisphosphonate treatment should be overseen by a paediatrician with expertise in genetic bone disease.

A recent Cochrane review of 819 participants from 14 trials, (2003-2013), showed a universal improvement in bone density but data on growth, bone pain, fracture incidence and function were incomplete(10). The studies included in this review were insufficiently powered to appropriately assess these secondary outcomes. Intravenous bisphosphonate treatment is associated with improvement in number of vertebral fractures in the growing skeleton and modeling (11) and some studies have shown a significant reduction in the incidence of long-bone fractures (12). In mild OI, oral bisphosphonates have been shown to reduce fracture rates to a similar degree to that of intravenous agents (12), but have neither been associated with improvements in spinal morphology nor reduction in bone pain(13).

Choice of regime

Not all children with OI require intravenous bisphosphonates. Treatment should be instigated in children with severe OI (e.g. type III), and strongly considered in children with two or more long-bone fractures per year, or children with vertebral compression fractures. Most data in OI pertains to use of pamidronate, with increasing data accumulating on use of other bisphosphonates, primarily zoledronate. The best agent, dose or frequency, are yet to be determined. Treatment approaches vary according to resources available and experience of the treating clinician. Pamidronate is often used under two years of age, followed by switching to zoledronate in older children with moderate to severe OI. A typical treatment approach is shown in Figure 1. Pamidronate doses vary from 9-12mg/kg/year and zoledronate is commenced at 0.1mg/kg/year in 2 divided doses. Many centres reduce the first ever dose of pamidronate (0.5mg/kg) or zoledronate (0.0125mg/kg or 0.025mg/kg) in bisphosphonate-naïve patients to minimize acute phase reactions and hypocalcemia. When bisphosphonate

treatment is ceased, there is no measurable effect on any subsequent bone formed (14). Ongoing treatment at reduced doses (as per recommendation above and Figure 1) is determined by a combination of fracture history, bone pain, bone mineral densitometry and growth(9). In general, once the height adjusted Z score is >0, then therapy should be reduced to 0.025mg/kg/year of zoledronic acid and 1.5mg/kg 6 monthly of pamidronate until the end of growth. It may be possible to cease treatment in children with OI type 1, however there remains no clear evidence with which to assist in these decisions, and this remains a controversial topic.

If the decision is made to cease at some point, re-institution of bisphosphonate can be considered when BMD starts to fall.

(1) (b) Idiopathic Juvenile Osteoporosis (IJO)

Recommendation: We recommend consideration of the use of bisphosphonates in severe forms of IJO (as evidenced by 2 or more long bone fragility fractures or vertebral fractures, consistent with the diagnosis of osteoporosis in paediatrics) (1,⊕⊕⊕⊕).

Evidence:

IJO is a primary bone disorder of unknown aetiology. It tends to affect young people in late childhood/early adolescence, and while it can result in recurrent long-bone and vertebral compression fractures, it is classically self-limiting. Residual long-bone and vertebral deformities can be disabling even once the bone mass has recovered. Given this, the use of bisphosphonates has been reported in this condition, with one RCT using Pamidronate. This study was limited by small sample size (n =5 in treatment group) but a reduction in fracture rate and bone pain in the treatment group was reported (15). There is no evidence to guide the duration of treatment, therefore we recommend the dose of bisphosphonate should be reduced after 2 years if height adjusted DXA scores are normalizing, as per the recommendations for Osteogenesis imperfecta outlined in figure 1.

(2) Secondary osteoporosis

There are many causes of secondary osteoporosis in childhood (Table 2).

Recommendations: Children with vertebral fracture(s) and/or low BMD and two or more long long-bone fractures, should be considered for intravenous bisphosphonate therapy (see Figure 2) (1,⊕⊕00).

Appropriate management of secondary osteoporosis also involves adequately addressing the underlying condition, together with consideration for reducing or ceasing osteotoxic medications where possible.

Bisphosphonates should only be used after attention to vitamin D status, calcium intake, physical therapies to maximise mobility and gonadal hormone treatment of absent, delayed or arrested puberty or late-presenting hypogonadism (1,⊕⊕00).

In general, prophylactic bisphosphonate therapy (that is, treating a low bone density Z score in the absence of fracture) is not recommended.

Evidence for bisphosphonate use in secondary osteoporosis:

(i) Cerebral palsy (CP) (Table 3):

Many factors result in low BMD and increased fracture in patients with CP including reduced mobility, poor nutrition, anticonvulsant use, limited sun exposure, later pubertal onset, pubertal arrest and late hypogonadism (16-18). Low trauma lower limb fractures predominate (19). The annual fracture rate in patients with CP is approximately 5%, double that of a normal age matched population (16, 20).

Bisphosphonates increase BMD in children with CP (21) (22-24), but there is a paucity of randomized controlled trials (16, 25) and very limited data on the effect of bisphosphonates in reducing fracture risk (26, 27). A recent review

concluded that bisphosphonates were probably effective at raising BMD, and possibly effective at decreasing fracture rate in this cohort(28).

Prophylactic bisphosphonate therapy (i.e., treating a low BMD Z-score in the absence of fracture) is difficult to justify in young people with CP, with no evidence supporting its use, and would rarely be considered outside the setting of severe pain presumed to be of bone origin.

There are limited data to guide recommendations for duration of treatment in children with CP. Twelve months of intravenous pamidronate has been shown to reduce fracture rate by almost 70%, four years after ceasing therapy and despite a return in BMD to pretreatment values(26). After treatment cessation, it is also worth considering that a continuing increase in BMD without treatment (such as during puberty), should reassure, and re – institution of bisphosphonate should be considered when BMD starts to fall. In general BMD assessment is problematic in this patient group and may not always be clinically useful. Given these factors and the clinical experience of the authors, we would recommend yearly evaluation of bone density where possible, and only treat beyond 2 years if there is ongoing fracture or bone pain (figure 2). This is, however, an area in need of further research.

(ii) Other forms of secondary osteoporosis:

The published evidence in non-CP related secondary osteoporosis is limited by few RCTs and heterogeneous groups studied. However there are reports of improved BMD and vertebral morphology in these groups, even if there is no clear evidence for reduction in fractures.

Several RCTs have been published across a number of conditions with risks for osteoporosis, including: juvenile arthritis (29); post renal transplant (30); nephropathy/glucocorticoids (31); Crohn's disease (32), and mixed cohorts of inflammatory disorders (33). All show some improvement in BMD using different bisphosphonates (oral and intravenous), but most only with a short duration of follow up, and none powered to explore the key outcome measure of fracture rate. Further small case control studies, with limited follow up, of

bisphosphonate use in inflammatory conditions, while heterogeneous, all support a positive effect of treatment (34-37).

All published studies in Duchenne Muscular Dystrophy are observational in nature, with a recent Cochrane review concluding there was no high quality RCT evidence to guide management(38) . Although limited in number and design, studies have shown maintenance/improvement in BMD (39, 40), increased survival (41), improved vertebral body shape and reduced pain (42). However there is some evidence that bone quality may be affected, with reduction in trabecular number on bone biopsy (43). Further studies are required to strengthen the evidence base but we would recommend therapy in the presence of fractures, particularly vertebral fractures which are very common in this patient group. If glucocorticoid therapy is accompanied by poor growth it may be possible to reduce the frequency of bisphosphonate therapy. There are however no data to support this recommendation. Consideration in DMD should be given to ongoing bisphosphonate treatment for longer periods than recommended in other conditions, whilst high dose corticosteroids continue to be administered. The vast majority of corticosteroid treated boys with DMD do not enter puberty spontaneously and we would recommend consideration of pubertal induction by age 14.

Limited case control data in bone marrow transplant patients with graft versus host disease showed increased BMD using bisphosphonates (44), while in a group with haematological malignancies, bisphosphonates reduced both BMD and bone pain compared to a control group (45).

Other studies have also shown improvement in vertebral body shape with bisphosphonate therapy in young people, including a mixed cohort of patients with low BMD and fracture (46), and a cohort with congenital neutropenia (47).

(3) Use of bisphosphonates in conditions other than skeletal fragility

Bisphosphonates have been trialed with varying effect in a wide range of conditions beyond skeletal fragility, including fibrous dysplasia, avascular necrosis, bone cysts/tumour/metastases, inflammatory conditions and generalized arterial calcification of infancy. Available evidence and recommendations are highlighted below.

Fibrous dysplasia (FD)

Recommendation: Intravenous bisphosphonates are effective to treat bone pain associated with fibrous dysplasia (1,⊕⊕00). Twenty-four months of therapy (pamidronate or zoledronate) can result in long-term pain control. Treatment duration may be limited by increase in BMD in normal adjacent bone. Bisphosphonates do not alter lesion size or expansion in long bones (1,⊕⊕00) but should be considered for progressive optic canal encroachment.

Evidence:

There is no evidence to suggest that bisphosphonates alter size or expansion of bony lesions in FD in children. Small observational studies, (48-54) with no control group, show variable responses, although there is good analgesic effect seen in most patients. One RCT using oral alendronate (55) showed variable results. When fibrous dysplasia is part of McCune-Albright Syndrome, untreated acromegaly has a major adverse effect on expansion of craniofacial FD and needs to be managed separately.

Avascular Necrosis (AVN)

Recommendation: Bisphosphonates can be considered for pain control in AVN. There is no convincing evidence for its effect in prevention of bony collapse (2,⊕000).

Evidence:

AVN in children can be idiopathic, occur after trauma, or follow corticosteroid administration. It may be confined to a single bone such as Perthes' disease of the hip, or can occur at multiple sites. Small observational studies in children suggest improvement in pain and prevention of collapse of femoral head following treatment with bisphosphonates (56-60), but RCTs are required in order to fully understand the role of bisphosphonates in AVN.

Bone cysts, bone tumour, skeletal metastases

Recommendation: There is limited evidence to show that bisphosphonates reduce pain or slow lesion progression in benign bone cysts. However, they may be considered in large/rapidly expanding lesions if conventional therapies have failed or are not feasible (2,⊕000).

Evidence:

Bisphosphonates have been used in treating aneurysmal bone cysts and benign bone tumours. A single case report (61) showed significant reduction in pain and lesion size after treating an aneurysmal bone cyst with zoledronate. Pain reduction was seen in five children with bone cysts (62) with variable responses in lesion size. The rarity of these lesions reduces the likelihood of improving the evidence base for bisphosphonate use.

Bisphosphonate therapy is used in adults, across many varieties of bony metastatic disease, to reduce pain and other skeletal events, such as fracture (e.g., breast cancer (63)). Observational evidence exists for effect of zoledronic acid on pain relief of metastatic disease in neuroblastoma and hepatoblastoma (64).

Inflammatory bone conditions:

Recommendation: Bisphosphonates are a potential second line therapy to reduce pain in chronic recurrent multifocal osteomyelitis (1,⊕000).

Evidence:

The use of bisphosphonates as second line agents in chronic recurrent multifocal osteomyelitis (CRMO) is limited to reports in four observational studies, with no control group. All showed reduced pain in the majority of patients (65), with 12 months of bisphosphonate therapy often resulting in sustained pain relief. One study showed improved lesion size (66), and two found improvement in vertebral morphology (67, 68).

Generalized arterial calcification of infancy (GACI)

Recommendation:

Bisphosphonate therapy can be considered in severe cases of GACI (1,⊕○○○).

Evidence:

Generalized arterial calcification of infancy if untreated is a generally fatal condition often caused by a mutation in *ENPP1*. However, there is observational evidence supporting a survival benefit of bisphosphonate therapy, with a variety of first and second generation bisphosphonates used(69). There has been some longer term evidence that, given the propensity to a hypophosphatemic rickets-type picture in this condition, that bisphosphonate use worsens skeletal outcomes(70). Newer targeted therapies are in development such as an ENPP1-Fc fusion protein(71), which would avoid these negative sequelae.

(4) Hypercalcaemia:

Recommendation:

When hypercalcaemia is refractory to dietary manipulation and intravenous hydration, low dose bisphosphonate can be considered (pamidronate at 0.25mg/kg or zoledronate at 0.0125mg/kg), with at least 48 hours between doses and serum calcium monitored closely for 72 hours. (1,⊕⊕00).

Evidence:

Bisphosphonates have been used in a wide variety of conditions that cause severe hypercalcaemia (72), with case series/observational data for its use in vitamin D toxicity (73, 74), immobilisation hypercalcaemia (75) and severe neonatal hyperparathyroidism (76). In addition, case reports are published for its use in subcutaneous fat necrosis (77), PTHrP associated hypercalcaemia of infancy (78) and Williams syndrome (79). Bisphosphonate use has also been reported in paediatric cancer patients with hypercalcaemia (80, 81), with a case control study showing improvement in patients treated with Pamidronate (82). Prior to administration it is important to make sure the child is rehydrated to limit the possibility of bisphosphonate induced renal damage.

With this limited evidence base in mind, we recommend consideration for initial use of a low dose 0.0125mg/kg zoledronic acid or 0.25mg/kg pamidronate therapy should be given, due to risk of rebound hypocalcaemia. Repeated dosing can be given at 1-2 weekly intervals if needed until underlying condition is controlled with reports of doses of pamidronate up to 2mg/kg(73) being used.

Side effects and monitoring for bisphosphonate therapy

First dose effects:

Recommendation: To minimise the risk of hypocalcaemia, serum vitamin D level should be >50nmol/L prior to the first infusion and adequate calcium intake maintained post infusion. Paracetamol and anti-nausea medication can be used to manage the acute phase symptoms. Administration of a reduced first ever dose of bisphosphonate may reduce these side-effects (1,⊕⊕00).

Evidence:

(i) Acute phase response

Up to 80% of patients develop a self-limiting acute phase response with flu-like symptoms (fever, bone pains, myalgia, nausea/vomiting) within 24-48 hours after the first infusion, lasting up to several days (83) and resolving with simple analgesia and fluids (84).

(ii) Hypocalcaemia/hypophosphatemia

Bisphosphonate-induced hypocalcaemia occurs due to osteoclast inhibition of bone resorption. Contributing factors are vitamin D deficiency (84), advanced renal disease, prolonged glucocorticoid use and sub-clinical hypoparathyroidism. Severe symptomatic hypocalcaemia is rare (85). Calcitriol use for three days post first dose may reduce severity of hypocalcaemia and can be considered (83). Encouraging an adequate dietary intake of calcium, with supplement use if this is not possible, is also advised. Hypophosphatemia may also occur due although routine supplementation of phosphate is not recommended in this setting.

Rare but serious postulated side effects of bisphosphonate therapy:

(i) Iritis

Recommendation:

Any child with a red or painful eye should have ophthalmologic examination to exclude iritis, especially in the presence of an underlying rheumatologic condition (1,⊕000).

Evidence:

Iritis has been reported in anecdotal case reports.

(ii) Atypical femoral fractures

Recommendation:

So called “atypical” femoral fractures in young people in bisphosphonates may not be drug-related (1,⊕⊕00) and therefore such fractures are not necessarily an indication for treatment cessation.

Evidence:

The adult literature reports an association of long term use of bisphosphonates with atypical subtrochanteric femoral fractures (86). There are very few reports of similar lesions in the paediatric skeleton (87, 88). Two recent reviews of cohorts of young people with OI call into question the possibility of “atypical” femoral fractures (89, 90).

(iii) Bisphosphonate-induced osteonecrosis of the jaw (ONJ)

Recommendation:

Dental review should be undertaken prior to first dose of bisphosphonate, with any invasive dental work to be completed before a first dose. A 6 – 12 monthly dental review while on bisphosphonate is advisable (91) (1,⊕⊕00).

Evidence: A published guideline has recommended 6 – 12 monthly dental review while on bisphosphonate (91). There are no published reports of ONJ occurring in childhood (92, 93).

(iv) Teratogenic effects

Recommendation:

Pregnancy should be avoided for 12 months after a dose of bisphosphonate. All post menarchal girls should have a pregnancy test prior to bisphosphonate administration (1,⊕000).

Evidence:

Concerns have been raised in animal models regarding potential teratogenicity of bisphosphonates (94, 95), due to their ability to cross the placenta and, potentially, disrupt skeletal development. In the small number of reports where bisphosphonates have been used prior to conception, no significant effects on the fetus have been noted (96, 97).

(v) Oesophagitis

Recommendation:

As per the above recommendations, the only indication where there is any evidence to support even consideration of oral bisphosphonates is mild-moderate osteogenesis imperfecta. Care should be taken when using oral bisphosphonates in young people due the risk of erosive oesophagitis. They should only be used in children who can reliably swallow a whole tablet with a glass of water and who do not have gastro-oesophageal reflux disease (1,⊕000).

Evidence:

This recommendation is based on the adult literature where this is well described, however it seems to be an uncommon finding in paediatric studies(13).

(vi) Delayed bone healing in children with osteogenesis imperfecta

Recommendation:

Where possible, bisphosphonate therapy should be withheld until there is evidence of callus formation at a site of fracture or osteotomy in children with osteogenesis imperfecta (1,⊕000).

Evidence:

A case control study has shown delayed osteotomy healing in children with OI following the commencement of intravenous pamidronate therapy(98). A more recent study did not show a delay in healing, attributed to a change in surgical

technique and the use of zoledronic acid(99). Further studies are required to clarify the risk of delayed bone healing in this cohort of children.

Contraindications for bisphosphonate therapy

Recommendation

Avoidance of bisphosphonates in the following circumstances:

- During pregnancy as discussed above
- Renal impairment - Given the renal excretion of bisphosphonates, extreme caution should be taken
- Conditions where the underlying nature of the disorder means that an impairment of resorption will only further increase skeletal fragility, such as hypophosphatasia, or with sclerotic lesions and high bone mass disorders.

Active rickets, where attention to the mineral deficits is required.

Contraindication to further doses of bisphosphonates

Recommendation:

Bisphosphonate therapy is ceased when the height adjusted BMD Z score exceeds +2 SD (1,⊕⊕00).

Evidence:

An osteopetrosis-like picture is reported to develop where excessive doses of bisphosphonates have been administered (70, 100). Appropriate monitoring and judicious use, as outlined in Figure 1, would avoid this complication.

Assessments during bisphosphonate use

Recommendation: see Table 4 (1,⊕000).

While there has been no proven teratogenicity in humans, we recommend performing a urinary or serum qualitative hCG prior to every dose in post-menarchal females given the limited evidence base, and the concerns raised in animal models.

Bone turnover markers, such as osteocalcin, collagen cross linking studies, Procollagen type 1 intact N terminal (P1NP) and deoxypyridinoline, are still predominantly research tools, although reference ranges are improving for paediatric age patients.

BMD using Dual energy Xray absorptiometry scanning is the only available surrogate measure of bone accrual, and should be undertaken prior to first dose and at annual intervals in order to assess response to treatment (Figure 1). However there are issues with availability of reference data in <3 yr olds, and also technical issues in patients with significant contractures and/or internal fixation.

Peripheral quantitative computerized tomography (pQCT) is another method of assessing bone density. It has been primarily used in the research setting and the clinical utility of these scans is yet to be fully elucidated. The ability to generate a true volumetric density, as well as assessing skeletal geometric parameters, means that it can complement DXA scanning in centres with experience in its use.

Imaging of lateral thoraco-lumbar spine by x-ray or vertebral morphology assessment by DXA, is important to assess for compression fractures. This is an integral part of bone fragility assessment and should be performed at baseline and as clinically indicated.

Regular clinical monitoring for those on bisphosphonates should include annual BMD assessment where feasible, Vitamin D assessment and general biochemistry.

Conclusion

Bisphosphonates remain the main therapeutic agent for young people with significant skeletal fragility, and are also useful in a small but important number of other clinical settings. Use of these agents should be undertaken in centres

with sufficient expertise, and with ongoing monitoring by a physician experienced in their effects. Further evidence is still required to strengthen many of the recommendations made in this guideline.

Table 1: Grade system of evidence (from Swiglo et al (5))

⊕000 (very low quality)	⊕⊕00 (low quality)	⊕⊕⊕0 (moderate quality)	⊕⊕⊕⊕ (high quality)
Unsystematic clinical observations, very indirect evidence	At least one observational study, RCTs with flaws, indirect evidence	RCTs with limitations, strong unbiased observational	Well performed RCTs, exceptionally strong unbiased observational studies

Table 2: Causes of secondary osteoporosis

Inflammatory	Immobility	Iatrogenic	Nutritional	Endocrine	Haematological/infiltrative
Inflammatory bowel disease	Cerebral palsy	Glucocorticoid therapy	Anorexia nervosa	hypogonadism	Malignancy
Juvenile idiopathic arthropathy	Neuromuscular dystrophy	Anti-epileptic drugs	Coeliac disease	Hyperthyroidism	Haemaglobinopathies
Other systemic inflammatory disorders	Spinal cord injury	GnRH agonist therapy	Protein calorie malnutrition (e.g. in elite athletes)	Cushing's Syndrome/Disease	
	Spina bifida	Warfarin	Cystic fibrosis	Growth hormone deficiency	
	Spinal-muscular atrophy		Other malabsorptive disorders	Hyperparathyroidism	

Table 3: Studies of bisphosphonate usage children with CP**(a) Study description**

	Study	Participants	Bisphosphonate	Supplements
Allington(22)	Prospective case series	n=11 (CP)	Pamidronate i/v: 1mg/kg for 3 days, every 4 months for 1 year	Calcium and vitamin D, dose not reported
Bachrach(26)	Retrospective case analysis	n=25 treated n=79 non-treated comparison group	Pamidronate i/v: 1 mg/kg/dose (maximum 35 mg) for three consecutive days every 3-4 months	Vitamin D supplementation if 25(OH)D<30 ng/dL
Henderson(16)	Double-blind, placebo controlled RCT	n=14 (7 intervention, 7 placebo)	Pamidronate i/v: 1mg/kg for 3 days, every 4 months for 1 year (not <15 mg or >30 mg per dose)	Calcium 1000 mg, vitamin D 400IU per day
Iwasaki(25)	Double-blind RCT	n=10 (vitamin D), n=10 (vitamin D and Risedronate)	Risedronate p/o for 6 months (dosage not reported)	Vitamin D dosage not reported
Plotkin(23)	Prospective case series	n=23	Pamidronate i/v: 0.75 mg/d for 2 days every 4 months for one year	Calcium and vitamin D 1 week prior to infusion as required
Shaw(24)	Case series	n=1 (Etidronate), n=2 (Pamidronate)	Etidronate p/o: 7.5 mg/kg for 2 days every 3 months for 1 year Pamidronate i/v: 0.4 mg/kg every 3 months for 1 year	Calcium 400 mg (elemental), Vitamin D 400 IU/day
Paksu(101)	Prospective case study	n=26	Aledronate p/o: 1mg/kg/week for one year	Calcium 600 mg, Vitamin D 400 IU/day

(b) Outcomes of studies from Table 2 (a) – NB Bachrach study from table two (a) had 2 cohorts and therefore 2 outcomes

	BMD on DXA in mean SDS (SD or SE) - before and after treatment						Clinical
	Lumbar-spine		p-value	Femur		p-value	
Allington(22)	n=18	Positive Z-score improvement statistically significant					Pain improved
Bachrach(102)	n=7	-4(0.4) to -2.8(0.3)	0.03	n=9	-3.6(0.4) to -1.7(0.9)	0.03	n/a
Bachrach(26)	n=25	No specific data. BMD returned to baseline within 2 years					Fracture reduced by 13%, p=0.02
Henderson(16)	n=6	-3.4(0.4) to -2.2(0.4)	0.005	n=6	-4(0.6) to -1.8(1)	0.01	n/a
Iwasaki(25)	n=20	Significant improvement in BMD					n/a
Plotkin(23)	n=19	-3.8(1.4) to -2.3(1.2)	<0.01	n=23	-4.5(1.2) to -2.6(0.9)	<0.01	n/a
Shaw(24)	n=3	Improvement in BMD Z-scores					n/a
Paksu(101)	n=26	-3.45(1) to -2.4(0.9)	<0.001	-	-	-	n/a

Table 4: Assessment to be undertaken before first dose of bisphosphonates

Full Blood Count
Urea and Electrolytes
Liver function tests
25 hydroxy Vitamin D
Parathyroid hormone
Calcium, magnesium, phosphate
Dental review

Figure 1: Flow chart for the use of bisphosphonates in a young person with severe Osteogenesis Imperfecta. Note: Optimize bone health - Optimize dietary calcium intake, ensure vitamin D sufficient, maximise weight bearing exercise. Other factors in assessment at 12 months: fracture rate, bone pain, mobility, other medications.

Figure 2: Flow chart for the use of bisphosphonates in a young person with secondary osteoporosis. Note: Optimize bone health - Optimize dietary calcium intake, ensure vitamin D sufficient, maximise weight bearing exercise. Other factors in assessment at 12 months: fracture rate, bone pain, mobility, other medications.

References

1. Weaver CM, Gordon CM, Janz KF, Kalkwarf HJ, Lappe JM, Lewis R, et al. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. *Osteoporos Int.* 2016;27(4):1281-386. doi: 10.1007/s00198-015-3440-3. PubMed PMID: 26856587; PubMed Central PMCID: PMC4791473.
2. Ward LM, Konji VN, Ma J. The management of osteoporosis in children. *Osteoporos Int.* 2016;27(7):2147-79. doi: 10.1007/s00198-016-3515-9. PubMed PMID: 27125514.
3. Bishop N, Arundel P, Clark E, Dimitri P, Farr J, Jones G, et al. Fracture prediction and the definition of osteoporosis in children and adolescents: the ISCD 2013 Pediatric Official Positions. *J Clin Densitom.* 2014;17(2):275-80. doi: 10.1016/j.jocd.2014.01.004. PubMed PMID: 24631254.
4. Bachrach LK, Ward LM. Clinical review 1: Bisphosphonate use in childhood osteoporosis. *J Clin Endocrinol Metab.* 2009;94(2):400-9. doi: 10.1210/jc.2008-1531. PubMed PMID: 19033370.
5. Swiglo BA, Murad MH, Schunemann HJ, Kunz R, Vigersky RA, Guyatt GH, et al. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab.* 2008;93(3):666-73. doi: 10.1210/jc.2007-1907. PubMed PMID: 18171699.
6. Rauch F, Travers R, Plotkin H, Glorieux FH. The effects of intravenous pamidronate on the bone tissue of children and adolescents with osteogenesis imperfecta. *J Clin Invest.* 2002;110(9):1293-9. doi: 10.1172/JCI15952. PubMed PMID: 12417568; PubMed Central PMCID: PMC151613.
7. Papapoulos SE, Cremers SC. Prolonged bisphosphonate release after treatment in children. *N Engl J Med.* 2007;356(10):1075-6. doi: 10.1056/NEJMc062792. PubMed PMID: 17347467.
8. Biggin A, Munns CF. Osteogenesis imperfecta: diagnosis and treatment. *Curr Osteoporos Rep.* 2014;12(3):279-88. doi: 10.1007/s11914-014-0225-0. PubMed PMID: 24964776.
9. Trejo P, Rauch F. Osteogenesis imperfecta in children and adolescents- new developments in diagnosis and treatment. *Osteoporos Int.* 2016;27(12):3427-37. doi: 10.1007/s00198-016-3723-3. PubMed PMID: 27492436.
10. Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. *Cochrane Database Syst Rev.* 2016;10:CD005088. doi: 10.1002/14651858.CD005088.pub4. PubMed PMID: 27760454.
11. Alcausin MB, Briody J, Pacey V, Ault J, McQuade M, Bridge C, et al. Intravenous pamidronate treatment in children with moderate-to-severe osteogenesis imperfecta started under three years of age. *Horm Res Paediatr.* 2013;79(6):333-40. doi: 10.1159/000351374. PubMed PMID: 23735642.
12. Shi CG, Zhang Y, Yuan W. Efficacy of Bisphosphonates on Bone Mineral Density and Fracture Rate in Patients With Osteogenesis Imperfecta: A Systematic Review and Meta-analysis. *Am J Ther.* 2016;23(3):e894-904. doi: 10.1097/MJT.0000000000000236. PubMed PMID: 25844482.

13. Bishop N, Adami S, Ahmed SF, Anton J, Arundel P, Burren CP, et al. Risedronate in children with osteogenesis imperfecta: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2013;382(9902):1424-32. doi: 10.1016/S0140-6736(13)61091-0. PubMed PMID: 23927913.
14. Rauch F, Cornibert S, Cheung M, Glorieux FH. Long-bone changes after pamidronate discontinuation in children and adolescents with osteogenesis imperfecta. *Bone*. 2007;40(4):821-7. doi: 10.1016/j.bone.2006.11.020. PubMed PMID: 17223617.
15. Baroncelli GI, Vierucci F, Bertelloni S, Erba P, Zampollo E, Giuca MR. Pamidronate treatment stimulates the onset of recovery phase reducing fracture rate and skeletal deformities in patients with idiopathic juvenile osteoporosis: comparison with untreated patients. *J Bone Miner Metab*. 2013;31(5):533-43. doi: 10.1007/s00774-013-0438-9. PubMed PMID: 23549954.
16. Henderson RC, Lark RK, Kecskemethy HH, Miller F, Harcke HT, Bachrach SJ. Bisphosphonates to treat osteopenia in children with quadriplegic cerebral palsy: a randomized, placebo-controlled clinical trial. *The Journal of pediatrics*. 2002;141(5):644-51. doi: 10.1067/mpd.2002.128207. PubMed PMID: 12410192.
17. Hough JP, Boyd RN, Keating JL. Systematic review of interventions for low bone mineral density in children with cerebral palsy. *Pediatrics*. 2010;125(3):e670-8. doi: 10.1542/peds.2009-0292. PubMed PMID: 20123765.
18. Trinh A, Fahey MC, Brown J, Fuller PJ, Milat F. Optimizing bone health in cerebral palsy across the lifespan. *Dev Med Child Neurol*. 2017;59(2):232-3. doi: 10.1111/dmcn.13355. PubMed PMID: 28044317.
19. Henderson RC, Berglund LM, May R, Zemel BS, Grossberg RI, Johnson J, et al. The relationship between fractures and DXA measures of BMD in the distal femur of children and adolescents with cerebral palsy or muscular dystrophy. *J Bone Miner Res*. 2010;25(3):520-6. doi: 10.1359/jbmr.091007. PubMed PMID: 19821773; PubMed Central PMCID: PMC3153393.
20. Munns CF, Cowell CT. Prevention and treatment of osteoporosis in chronically ill children. *Journal of musculoskeletal & neuronal interactions*. 2005;5(3):262-72. PubMed PMID: 16172517.
21. Iwasaki T, Nonoda Y, Ishii M. Long-term outcomes of children and adolescents who had cerebral palsy with secondary osteoporosis. *Current medical research and opinion*. 2012;28(5):737-47. doi: 10.1185/03007995.2011.645562. PubMed PMID: 22126423.
22. Allington N, Vivegnis D, Gerard P. Cyclic administration of pamidronate to treat osteoporosis in children with cerebral palsy or a neuromuscular disorder: a clinical study. *Acta orthopaedica Belgica*. 2005;71(1):91-7. PubMed PMID: 15792214.
23. Plotkin H, Coughlin S, Kreikemeier R, Heldt K, Bruzoni M, Lerner G. Low doses of pamidronate to treat osteopenia in children with severe cerebral palsy: a pilot study. *Developmental medicine and child neurology*. 2006;48(9):709-12. doi: 10.1017/S0012162206001526. PubMed PMID: 16904014.
24. Shaw NJ, White CP, Fraser WD, Rosenbloom L. Osteopenia in cerebral palsy. *Archives of disease in childhood*. 1994;71(3):235-8. PubMed PMID: 7979497; PubMed Central PMCID: PMC1029978.
25. Iwasaki T, Takei K, Nakamura S, Hosoda N, Yokota Y, Ishii M. Secondary osteoporosis in long-term bedridden patients with cerebral palsy. *Pediatrics*

- international : official journal of the Japan Pediatric Society. 2008;50(3):269-75. doi: 10.1111/j.1442-200X.2008.02571.x. PubMed PMID: 18533934.
26. Bachrach SJ, Kecskemethy HH, Harcke HT, Hossain J. Decreased fracture incidence after 1 year of pamidronate treatment in children with spastic quadriplegic cerebral palsy. *Dev Med Child Neurol*. 2010;52(9):837-42. doi: 10.1111/j.1469-8749.2010.03676.x. PubMed PMID: 20573180.
27. Sees JP, Sitoula P, Dabney K, Holmes L, Jr., Rogers KJ, Kecskemethy HH, et al. Pamidronate Treatment to Prevent Reoccurring Fractures in Children With Cerebral Palsy. *J Pediatr Orthop*. 2016;36(2):193-7. doi: 10.1097/BPO.0000000000000421. PubMed PMID: 25757207.
28. Ozel S, Switzer L, Macintosh A, Fehlings D. Informing evidence-based clinical practice guidelines for children with cerebral palsy at risk of osteoporosis: an update. *Dev Med Child Neurol*. 2016;58(9):918-23. doi: 10.1111/dmcn.13196. PubMed PMID: 27435427.
29. Lepore L, Pennesi M, Barbi E, Pozzi R. Treatment and prevention of osteoporosis in juvenile chronic arthritis with disodium clodronate. *Clin Exp Rheumatol*. 1991;9 Suppl 6:33-5. PubMed PMID: 2060176.
30. El-Husseini AA, El-Agroudy AE, El-Sayed MF, Sobh MA, Ghoneim MA. Treatment of osteopenia and osteoporosis in renal transplant children and adolescents. *Pediatr Transplant*. 2004;8(4):357-61. doi: 10.1111/j.1399-3046.2004.00191.x. PubMed PMID: 15265162.
31. Kim SD, Cho BS. Pamidronate therapy for preventing steroid-induced osteoporosis in children with nephropathy. *Nephron Clin Pract*. 2006;102(3-4):c81-7. doi: 10.1159/000089664. PubMed PMID: 16282699.
32. Sbrocchi AM, Forget S, Laforte D, Azouz EM, Rodd C. Zoledronic acid for the treatment of osteopenia in pediatric Crohn's disease. *Pediatr Int*. 2010;52(5):754-61. doi: 10.1111/j.1442-200X.2010.03174.x. PubMed PMID: 20524999.
33. Rudge S, Hailwood S, Horne A, Lucas J, Wu F, Cundy T. Effects of once-weekly oral alendronate on bone in children on glucocorticoid treatment. *Rheumatology (Oxford)*. 2005;44(6):813-8. doi: 10.1093/rheumatology/keh538. PubMed PMID: 15695300.
34. Grenda R, Karczarewicz E, Rubik J, Matusik H, Pludowski P, Kiliszek M, et al. Bone mineral disease in children after renal transplantation in steroid-free and steroid-treated patients--a prospective study. *Pediatr Transplant*. 2011;15(2):205-13. doi: 10.1111/j.1399-3046.2010.01448.x. PubMed PMID: 21199211.
35. Acott PD, Wong JA, Lang BA, Crocker JF. Pamidronate treatment of pediatric fracture patients on chronic steroid therapy. *Pediatr Nephrol*. 2005;20(3):368-73. doi: 10.1007/s00467-004-1790-8. PubMed PMID: 15690187.
36. Bianchi ML, Cimaz R, Bardare M, Zulian F, Lepore L, Boncompagni A, et al. Efficacy and safety of alendronate for the treatment of osteoporosis in diffuse connective tissue diseases in children: a prospective multicenter study. *Arthritis Rheum*. 2000;43(9):1960-6. doi: 10.1002/1529-0131(200009)43:9<1960::AID-ANR6>3.0.CO;2-J. PubMed PMID: 11014345.
37. Inoue Y, Shimojo N, Suzuki S, Arima T, Tomiita M, Minagawa M, et al. Efficacy of intravenous alendronate for the treatment of glucocorticoid-induced osteoporosis in children with autoimmune diseases. *Clin Rheumatol*.

- 2008;27(7):909-12. doi: 10.1007/s10067-008-0864-6. PubMed PMID: 18330609.
38. Bell JM, Shields MD, Watters J, Hamilton A, Beringer T, Elliott M, et al. Interventions to prevent and treat corticosteroid-induced osteoporosis and prevent osteoporotic fractures in Duchenne muscular dystrophy. *Cochrane Database Syst Rev*. 2017;1:CD010899. doi: 10.1002/14651858.CD010899.pub2. PubMed PMID: 28117876.
39. Hawker GA, Ridout R, Harris VA, Chase CC, Fielding LJ, Biggar WD. Alendronate in the treatment of low bone mass in steroid-treated boys with Duchennes muscular dystrophy. *Arch Phys Med Rehabil*. 2005;86(2):284-8. doi: 10.1016/j.apmr.2004.04.021. PubMed PMID: 15706555.
40. Houston C, Mathews K, Shibli-Rahhal A. Bone density and alendronate effects in Duchenne muscular dystrophy patients. *Muscle Nerve*. 2014;49(4):506-11. doi: 10.1002/mus.23948. PubMed PMID: 23835890.
41. Gordon KE, Dooley JM, Sheppard KM, MacSween J, Esser MJ. Impact of bisphosphonates on survival for patients with Duchenne muscular dystrophy. *Pediatrics*. 2011;127(2):e353-8. doi: 10.1542/peds.2010-1666. PubMed PMID: 21242224.
42. Sbrocchi AM, Rauch F, Jacob P, McCormick A, McMillan HJ, Matzinger MA, et al. The use of intravenous bisphosphonate therapy to treat vertebral fractures due to osteoporosis among boys with Duchenne muscular dystrophy. *Osteoporos Int*. 2012;23(11):2703-11. doi: 10.1007/s00198-012-1911-3. PubMed PMID: 22297733.
43. Misof BM, Roschger P, McMillan HJ, Ma J, Klaushofer K, Rauch F, et al. Histomorphometry and Bone Matrix Mineralization Before and After Bisphosphonate Treatment in Boys With Duchenne Muscular Dystrophy: A Paired Transiliac Biopsy Study. *J Bone Miner Res*. 2016;31(5):1060-9. doi: 10.1002/jbmr.2756. PubMed PMID: 26615086.
44. Carpenter PA, Hoffmeister P, Chesnut CH, 3rd, Storer B, Charuhas PM, Woolfrey AE, et al. Bisphosphonate therapy for reduced bone mineral density in children with chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2007;13(6):683-90. doi: 10.1016/j.bbmt.2007.02.001. PubMed PMID: 17531778.
45. Lee JM, Kim JE, Bae SH, Hah JO. Efficacy of pamidronate in children with low bone mineral density during and after chemotherapy for acute lymphoblastic leukemia and non-Hodgkin lymphoma. *Blood Res*. 2013;48(2):99-106. doi: 10.5045/br.2013.48.2.99. PubMed PMID: 23826578; PubMed Central PMCID: PMC3698414.
46. Simm PJ, Johannesen J, Briody J, McQuade M, Hsu B, Bridge C, et al. Zoledronic acid improves bone mineral density, reduces bone turnover and improves skeletal architecture over 2 years of treatment in children with secondary osteoporosis. *Bone*. 2011;49(5):939-43. doi: 10.1016/j.bone.2011.07.031. PubMed PMID: 21820091.
47. Borzutzky A, Reyes ML, Figueroa V, Garcia C, Cavieres M. Osteoporosis in children with severe congenital neutropenia: bone mineral density and treatment with bisphosphonates. *J Pediatr Hematol Oncol*. 2006;28(4):205-9. doi: 10.1097/01.mph.0000210409.48877.c3. PubMed PMID: 16679916.
48. Matarazzo P, Lala R, Masi G, Andreo M, Altare F, de Sanctis C. Pamidronate treatment in bone fibrous dysplasia in children and adolescents with McCune-

- Albright syndrome. *J Pediatr Endocrinol Metab.* 2002;15 Suppl 3:929-37. PubMed PMID: 12199352.
49. Lala R, Matarazzo P, Bertelloni S, Buzi F, Rigon F, de Sanctis C. Pamidronate treatment of bone fibrous dysplasia in nine children with McCune-Albright syndrome. *Acta Paediatr.* 2000;89(2):188-93. PubMed PMID: 10709889.
50. Lala R, Matarazzo P, Andreo M, Marzari D, Bellone J, Corrias A, et al. Bisphosphonate treatment of bone fibrous dysplasia in McCune-Albright syndrome. *J Pediatr Endocrinol Metab.* 2006;19 Suppl 2:583-93. PubMed PMID: 16789621.
51. Plotkin H, Rauch F, Zeitlin L, Munns C, Travers R, Glorieux FH. Effect of pamidronate treatment in children with polyostotic fibrous dysplasia of bone. *J Clin Endocrinol Metab.* 2003;88(10):4569-75. doi: 10.1210/jc.2003-030050. PubMed PMID: 14557424.
52. Kos M, Luczak K, Godzinski J, Klempous J. Treatment of monostotic fibrous dysplasia with pamidronate. *J Craniomaxillofac Surg.* 2004;32(1):10-5. PubMed PMID: 14729043.
53. Chapurlat RD, Huguency P, Delmas PD, Meunier PJ. Treatment of fibrous dysplasia of bone with intravenous pamidronate: long-term effectiveness and evaluation of predictors of response to treatment. *Bone.* 2004;35(1):235-42. doi: 10.1016/j.bone.2004.03.004. PubMed PMID: 15207763.
54. Chan B, Zacharin M. Pamidronate treatment of polyostotic fibrous dysplasia: failure to prevent expansion of dysplastic lesions during childhood. *J Pediatr Endocrinol Metab.* 2006;19(1):75-80. PubMed PMID: 16509531.
55. Boyce AM, Kelly MH, Brillante BA, Kushner H, Wientroub S, Riminucci M, et al. A randomized, double blind, placebo-controlled trial of alendronate treatment for fibrous dysplasia of bone. *J Clin Endocrinol Metab.* 2014;99(11):4133-40. doi: 10.1210/jc.2014-1371. PubMed PMID: 25033066; PubMed Central PMCID: PMC4223439.
56. McQuade M, Houghton K. Use of bisphosphonates in a case of Perthes disease. *Orthop Nurs.* 2005;24(6):393-8. PubMed PMID: 16319725.
57. Ramachandran M, Ward K, Brown RR, Munns CF, Cowell CT, Little DG. Intravenous bisphosphonate therapy for traumatic osteonecrosis of the femoral head in adolescents. *J Bone Joint Surg Am.* 2007;89(8):1727-34. doi: 10.2106/JBJS.F.00964. PubMed PMID: 17671011.
58. Nguyen T, Zacharin MR. Pamidronate treatment of steroid associated osteonecrosis in young patients treated for acute lymphoblastic leukaemia--two-year outcomes. *J Pediatr Endocrinol Metab.* 2006;19(2):161-7. PubMed PMID: 16562590.
59. Kotecha RS, Powers N, Lee SJ, Murray KJ, Carter T, Cole C. Use of bisphosphonates for the treatment of osteonecrosis as a complication of therapy for childhood acute lymphoblastic leukaemia (ALL). *Pediatr Blood Cancer.* 2010;54(7):934-40. doi: 10.1002/pbc.22428. PubMed PMID: 20127847.
60. Padhye B, Dalla-Pozza L, Little DG, Munns CF. Use of zoledronic acid for treatment of chemotherapy related osteonecrosis in children and adolescents: a retrospective analysis. *Pediatr Blood Cancer.* 2013;60(9):1539-45. doi: 10.1002/pbc.24563. PubMed PMID: 23625773.
61. Simm PJ, O'Sullivan M, Zacharin MR. Successful treatment of a sacral aneurysmal bone cyst with zoledronic acid. *J Pediatr Orthop.* 2013;33(5):e61-4. doi: 10.1097/BPO.0b013e318285c3a7. PubMed PMID: 23752163.

62. Cornelis F, Truchetet ME, Amoretti N, Verdier D, Fournier C, Pillet O, et al. Bisphosphonate therapy for unresectable symptomatic benign bone tumors: a long-term prospective study of tolerance and efficacy. *Bone*. 2014;58:11-6. doi: 10.1016/j.bone.2013.10.004. PubMed PMID: 24120668.
63. Wong MH, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. *Cochrane Database Syst Rev*. 2012(2):CD003474. doi: 10.1002/14651858.CD003474.pub3. PubMed PMID: 22336790.
64. Joshi KZ, M.R. Bisphosphonate use for control of chronic severe bone pain in children with malignancy associated bone involvement. *European Society for Paediatric Endocrinology; Paris: Hormone Research in Paediatrics*; 2016.
65. Kerrison C, Davidson JE, Cleary AG, Beresford MW. Pamidronate in the treatment of childhood SAPHO syndrome. *Rheumatology (Oxford)*. 2004;43(10):1246-51. doi: 10.1093/rheumatology/keh295. PubMed PMID: 15238641.
66. Simm PJ, Allen RC, Zacharin MR. Bisphosphonate treatment in chronic recurrent multifocal osteomyelitis. *J Pediatr*. 2008;152(4):571-5. doi: 10.1016/j.jpeds.2007.08.047. PubMed PMID: 18346517.
67. Gleeson H, Wiltshire E, Briody J, Hall J, Chaitow J, Sillence D, et al. Childhood chronic recurrent multifocal osteomyelitis: pamidronate therapy decreases pain and improves vertebral shape. *J Rheumatol*. 2008;35(4):707-12. PubMed PMID: 18381777.
68. Hospach T, Langendoerfer M, von Kalle T, Maier J, Dannecker GE. Spinal involvement in chronic recurrent multifocal osteomyelitis (CRMO) in childhood and effect of pamidronate. *Eur J Pediatr*. 2010;169(9):1105-11. doi: 10.1007/s00431-010-1188-5. PubMed PMID: 20339868.
69. Rutsch F, Boyer P, Nitschke Y, Ruf N, Lorenz-Depierreux B, Wittkamp T, et al. Hypophosphatemia, hyperphosphaturia, and bisphosphonate treatment are associated with survival beyond infancy in generalized arterial calcification of infancy. *Circ Cardiovasc Genet*. 2008;1(2):133-40. doi: 10.1161/CIRCGENETICS.108.797704. PubMed PMID: 20016754; PubMed Central PMCID: PMC2794045.
70. Otero JE, Gottesman GS, McAlister WH, Mumm S, Madson KL, Kiffer-Moreira T, et al. Severe skeletal toxicity from protracted etidronate therapy for generalized arterial calcification of infancy. *J Bone Miner Res*. 2013;28(2):419-30. doi: 10.1002/jbmr.1752. PubMed PMID: 22972716.
71. Albright RA, Stabach P, Cao W, Kavanagh D, Mullen I, Braddock AA, et al. ENPP1-Fc prevents mortality and vascular calcifications in rodent model of generalized arterial calcification of infancy. *Nat Commun*. 2015;6:10006. doi: 10.1038/ncomms10006. PubMed PMID: 26624227; PubMed Central PMCID: PMC4686714.
72. Lteif AN, Zimmerman D. Bisphosphonates for treatment of childhood hypercalcemia. *Pediatrics*. 1998;102(4 Pt 1):990-3. PubMed PMID: 9755274.
73. Kara C, Cetinkaya S, Gunduz S, Can YLG, Aycan Z, Ayd NM. Efficacy and safety of pamidronate in children with vitamin D intoxication. *Pediatr Int*. 2015. doi: 10.1111/ped.12875. PubMed PMID: 26646324.
74. Sagsak E, Savas-Erdeve S, Keskin M, Cetinkaya S, Aycan Z. The use of pamidronate for acute vitamin D intoxication, clinical experience with three cases. *J Pediatr Endocrinol Metab*. 2015;28(5-6):709-12. doi: 10.1515/jpem-2014-0279. PubMed PMID: 25581744.

75. Kedlaya D, Brandstater ME, Lee JK. Immobilization hypercalcemia in incomplete paraplegia: successful treatment with pamidronate. *Arch Phys Med Rehabil.* 1998;79(2):222-5. PubMed PMID: 9474008.
76. Waller S, Kurzawinski T, Spitz L, Thakker R, Cranston T, Pearce S, et al. Neonatal severe hyperparathyroidism: genotype/phenotype correlation and the use of pamidronate as rescue therapy. *Eur J Pediatr.* 2004;163(10):589-94. doi: 10.1007/s00431-004-1491-0. PubMed PMID: 15241688.
77. Lombardi G, Cabano R, Bollani L, Del Forno C, Stronati M. Effectiveness of pamidronate in severe neonatal hypercalcemia caused by subcutaneous fat necrosis: a case report. *Eur J Pediatr.* 2009;168(5):625-7. doi: 10.1007/s00431-008-0797-8. PubMed PMID: 18726115.
78. Buckmaster A, Rodda C, Cowell CT, Ogle G, Dorney S. The use of pamidronate in PTHrP associated hypercalcaemia in infancy. *J Pediatr Endocrinol Metab.* 1997;10(3):301-4. PubMed PMID: 9388823.
79. Cagle AP, Waguespack SG, Buckingham BA, Shankar RR, Dimeglio LA. Severe infantile hypercalcemia associated with Williams syndrome successfully treated with intravenously administered pamidronate. *Pediatrics.* 2004;114(4):1091-5. doi: 10.1542/peds.2003-1146-L. PubMed PMID: 15466114.
80. Andiran N, Alikasifoglu A, Kupeli S, Yetgin S. Use of bisphosphonates for resistant hypercalcemia in children with acute lymphoblastic leukemia: report of two cases and review of the literature. *Turk J Pediatr.* 2006;48(3):248-52. PubMed PMID: 17172070.
81. Kerdudo C, Aerts I, Fattet S, Chevret L, Pacquement H, Doz F, et al. Hypercalcemia and childhood cancer: a 7-year experience. *J Pediatr Hematol Oncol.* 2005;27(1):23-7. PubMed PMID: 15654274.
82. Inukai T, Hirose K, Inaba T, Kurosawa H, Hama A, Inada H, et al. Hypercalcemia in childhood acute lymphoblastic leukemia: frequent implication of parathyroid hormone-related peptide and E2A-HLF from translocation 17;19. *Leukemia.* 2007;21(2):288-96. doi: 10.1038/sj.leu.2404496. PubMed PMID: 17183364.
83. Munns CF, Rajab MH, Hong J, Briody J, Hogler W, McQuade M, et al. Acute phase response and mineral status following low dose intravenous zoledronic acid in children. *Bone.* 2007;41(3):366-70. doi: 10.1016/j.bone.2007.05.002. PubMed PMID: 17574945.
84. Srivastava T, Dai H, Haney CJ, Alon US. Serum 25-hydroxyvitamin D level and acute-phase reaction following initial intravenous bisphosphonate. *J Bone Miner Res.* 2011;26(2):437-8. doi: 10.1002/jbmr.290. PubMed PMID: 21254232.
85. George S, Weber DR, Kaplan P, Hummel K, Monk HM, Levine MA. Short-Term Safety of Zoledronic Acid in Young Patients With Bone Disorders: An Extensive Institutional Experience. *J Clin Endocrinol Metab.* 2015;100(11):4163-71. doi: 10.1210/jc.2015-2680. PubMed PMID: 26308295; PubMed Central PMCID: PMC4702447.
86. Rizzoli R, Akesson K, Bouxsein M, Kanis JA, Napoli N, Papapoulos S, et al. Subtrochanteric fractures after long-term treatment with bisphosphonates: a European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation Working Group Report. *Osteoporos Int.* 2011;22(2):373-90. doi: 10.1007/s00198-010-1453-5. PubMed PMID: 21085935; PubMed Central PMCID: PMC3020314.

87. van de Laarschot DM, Zillikens MC. Atypical femur fracture in an adolescent boy treated with bisphosphonates for X-linked osteoporosis based on PLS3 mutation. *Bone*. 2016;91:148-51. doi: 10.1016/j.bone.2016.07.022. PubMed PMID: 27477003.
88. Boyce AM, Collins MT, Tosi LL, Gafni RI. A Subtrochanteric Femoral Stress Fracture following Bisphosphonate Treatment in an Adolescent Girl. *Horm Res Paediatr*. 2017;87(1):69-72. doi: 10.1159/000447425. PubMed PMID: 27379824; PubMed Central PMCID: PMC5218986.
89. Trejo P, Fassier F, Glorieux FH, Rauch F. Diaphyseal Femur Fractures in Osteogenesis Imperfecta: Characteristics and Relationship With Bisphosphonate Treatment. *J Bone Miner Res*. 2016. doi: 10.1002/jbmr.3071. PubMed PMID: 28019684.
90. Vuorimies I, Mayranpaa MK, Valta H, Kroger H, Toiviainen-Salo S, Makitie O. Bisphosphonate Treatment and the Characteristics of Femoral Fractures in Children With Osteogenesis Imperfecta. *J Clin Endocrinol Metab*. 2017;102(4):1333-9. doi: 10.1210/jc.2016-3745. PubMed PMID: 28323993.
91. Bhatt RN, Hibbert SA, Munns CF. The use of bisphosphonates in children: review of the literature and guidelines for dental management. *Aust Dent J*. 2014;59(1):9-19. doi: 10.1111/adj.12140. PubMed PMID: 24495226.
92. Brown JJ, Ramalingam L, Zacharin MR. Bisphosphonate-associated osteonecrosis of the jaw: does it occur in children? *Clin Endocrinol (Oxf)*. 2008;68(6):863-7. doi: 10.1111/j.1365-2265.2008.03189.x. PubMed PMID: 18221397.
93. Chahine C, Cheung MS, Head TW, Schwartz S, Glorieux FH, Rauch F. Tooth extraction socket healing in pediatric patients treated with intravenous pamidronate. *J Pediatr*. 2008;153(5):719-20. doi: 10.1016/j.jpeds.2008.05.003. PubMed PMID: 18940358.
94. Graepel P, Bentley P, Fritz H, Miyamoto M, Slater SR. Reproduction toxicity studies with pamidronate. *Arzneimittelforschung*. 1992;42(5):654-67. PubMed PMID: 1530681.
95. Patlas N, Golomb G, Yaffe P, Pinto T, Breuer E, Ornoy A. Transplacental effects of bisphosphonates on fetal skeletal ossification and mineralization in rats. *Teratology*. 1999;60(2):68-73. doi: 10.1002/(SICI)1096-9926(199908)60:2<68::AID-TERA10>3.0.CO;2-H. PubMed PMID: 10440778.
96. Munns CF, Rauch F, Ward L, Glorieux FH. Maternal and fetal outcome after long-term pamidronate treatment before conception: a report of two cases. *J Bone Miner Res*. 2004;19(10):1742-5. doi: 10.1359/JBMR.040711. PubMed PMID: 15355570.
97. Green SB, Pappas AL. Effects of maternal bisphosphonate use on fetal and neonatal outcomes. *Am J Health Syst Pharm*. 2014;71(23):2029-36. doi: 10.2146/ajhp140041. PubMed PMID: 25404594.
98. Munns CF, Rauch F, Zeitlin L, Fassier F, Glorieux FH. Delayed osteotomy but not fracture healing in pediatric osteogenesis imperfecta patients receiving pamidronate. *J Bone Miner Res*. 2004;19(11):1779-86. doi: 10.1359/JBMR.040814. PubMed PMID: 15476577.
99. Anam EA, Rauch F, Glorieux FH, Fassier F, Hamdy R. Osteotomy Healing in Children With Osteogenesis Imperfecta Receiving Bisphosphonate Treatment. *J Bone Miner Res*. 2015;30(8):1362-8. doi: 10.1002/jbmr.2486. PubMed PMID: 25708939.

100. Whyte MP, Wenkert D, Clements KL, McAlister WH, Mumm S. Bisphosphonate-induced osteopetrosis. *N Engl J Med*. 2003;349(5):457-63. doi: 10.1056/NEJMoa023110. PubMed PMID: 12890844.
101. Paksu MS, Vurucu S, Karaoglu A, Karacalioglu AO, Polat A, Yesilyurt O, et al. Osteopenia in children with cerebral palsy can be treated with oral alendronate. *Childs Nerv Syst*. 2012;28(2):283-6. doi: 10.1007/s00381-011-1576-9. PubMed PMID: 21928064.
102. Bachrach SJ, Kecskemethy HH, Harcke HT, Lark RK, Miller F, Henderson RC. Pamidronate treatment and posttreatment bone density in children with spastic quadriplegic cerebral palsy. *Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry*. 2006;9(2):167-74. doi: 10.1016/j.jocd.2005.11.003. PubMed PMID: 16785077.

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