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

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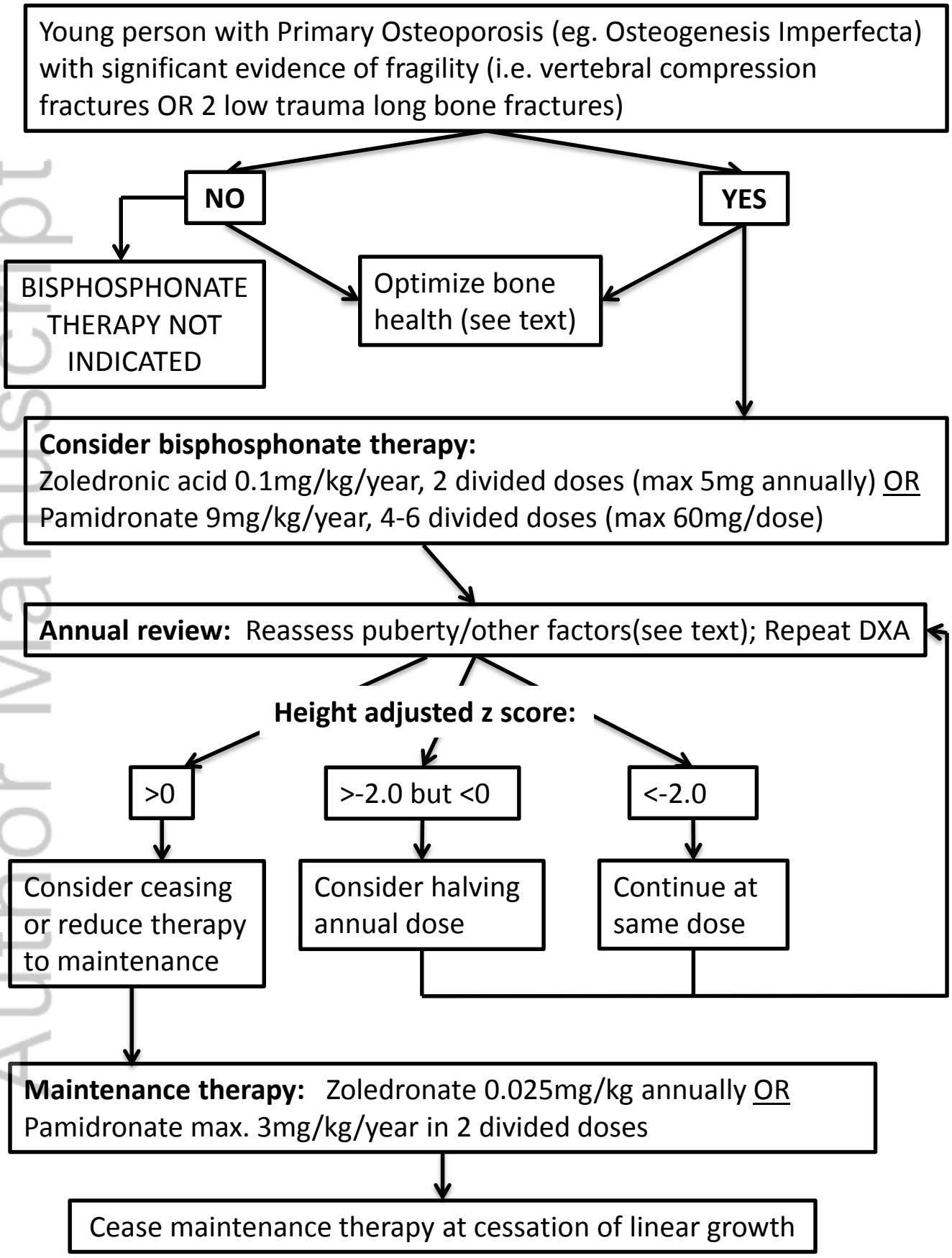

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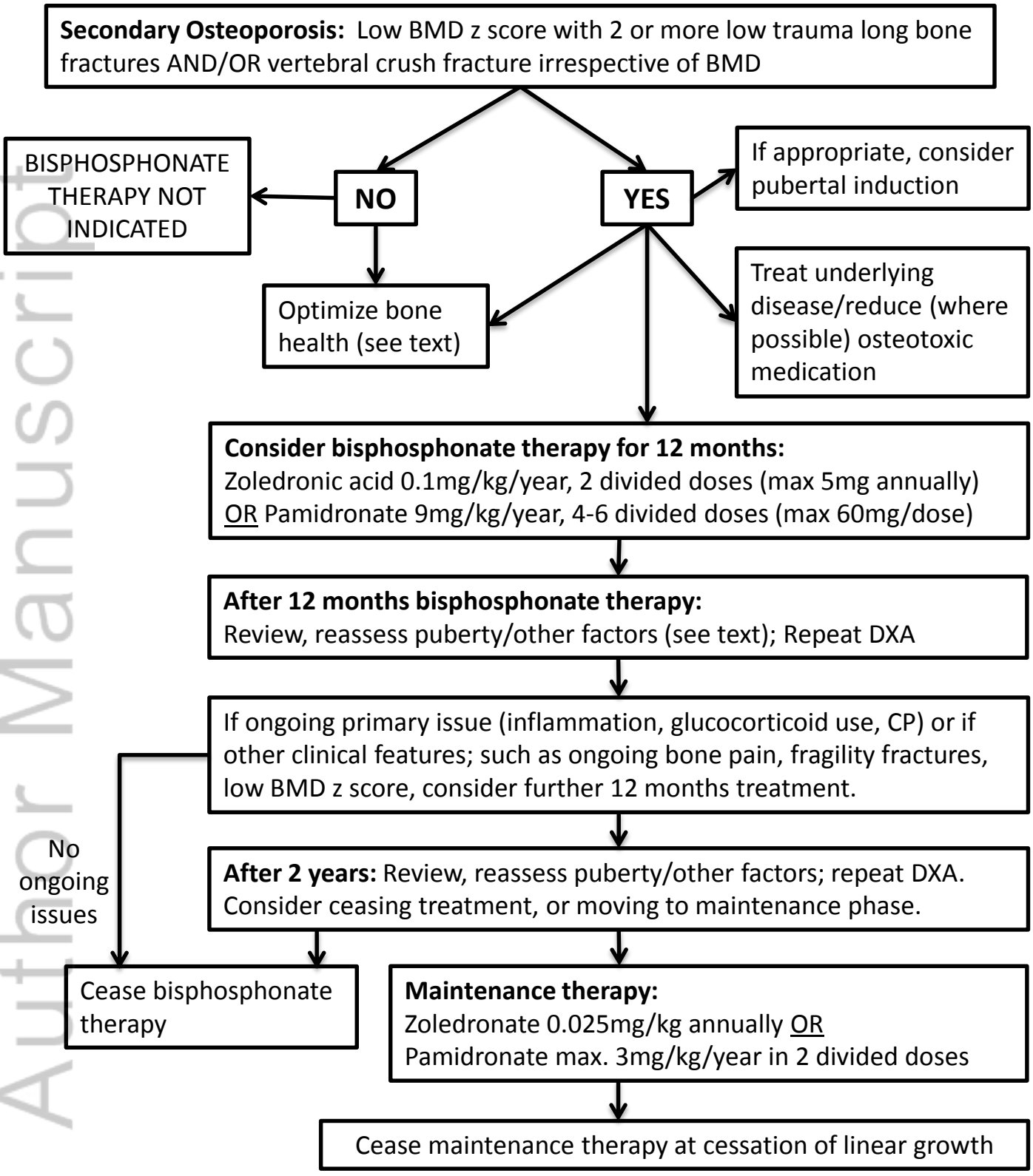

NB. If risk factors for low BMD persist (e.g., persistent chronic illness, ongoing glucocorticoid therapy) consider biannual DXA scan with possibility for top up dose of bisphosphonate if BMD is falling

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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.

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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 disroders, 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, elevatedcytokines, 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,

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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).

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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.

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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 be only be considered for those with mild-moderate OI in the absence of vertebral compression fractures (1,⊕⊕⊕O).

As outlined below, we would notrecommend 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,⊕OOO).

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)).

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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 0.025mgkg) in bisphosphonate-naïve patients to minimize acute phase reactions and hypocalcemia. When bisphosphonate

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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,⊕⊕OO).

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 normalzing, as per the recommendations for Osteogenesis imperfecta outlined in figure 1.

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(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,⊕⊕OO).

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,⊕⊕OO).

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

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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

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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).

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(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,⊕⊕OO). 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,⊕⊕OO) 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,⊕OOO).

Evidence:

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AVN in children can be idiopathic, occur after trauma, or follow corticosteroid administration. It may be confined to a single bone such 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,⊕OOO).

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,⊕OOO).

Evidence:

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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,⊕OOO).

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 hypophospatemic 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.

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(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,⊕⊕OO).

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.

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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,⊕⊕OO).

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,⊕OOO).

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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,⊕⊕OO) 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,⊕⊕OO).

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,⊕OOO).

Evidence:

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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,⊕OOO).

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,⊕OOO).

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

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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,⊕⊕OO).

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,⊕OOO).

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.

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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

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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.

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

⊕OOO (very low quality)	⊕⊕OO (low quality)	⊕⊕⊕O (moderate quality)	⊕⊕⊕⊕ (high quality)
Unsystematic clinical observations, very indirect evidence	At least one observational study, RCTs with flaws, indirect eveince	RCTs with limitations, strong unbiased observational	Well performed RCTs, exceptionally strong unbisaed observational studies

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Table 2: Causes of secondary osteoporosis

Inflammatory	**Immobility**	**Iatrogenic**	**Nutritional**	**Endocrine**	**Haematological/inflitrative**
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 atheletes)	Cushing‘s Syndrome/Disease	
	Spina bifida	Warfarin	Cystic fibrosis	Growth hormone deficiency	
	Spinal-muscular atrophy		Other malabsorptive disorders	Hyperparathyroidism	

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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

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(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

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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

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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.

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