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CONSENSUS STATEMENT

Hypophosphatasia: Canadian update on diagnosis and management

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Abstract

Summary Hypophosphatasia (HPP) is a rare inherited disorder of bone and mineral metabolism caused by loss of function mutations in the ALPL gene. The presentation in children and adults can be extremely variable and natural history is poorly understood particularly in adults. Careful patient evaluation is required with consideration of pharmacologic intervention in individuals meeting criteria for therapy.

Introduction The purposes of this review are to present current evidence regarding the diagnosis and management of hypophosphatasia in children and adults and provide evidence-based recommendations for management.

Method A MEDLINE, EMBASE, and Cochrane database search and literature review was completed. The following consensus recommendations were developed based on the highest level of evidence as well as expert opinion.

Results Hypophosphatasia is a rare inherited disorder of bone and mineral metabolism due to loss of function mutations in the tissue non-specific alkaline phosphatase (ALPL) gene causing reductions in the activity of the tissue non-specific isoenzyme of alkaline phosphatase (TNSALP). Deficient levels of alkaline phosphatase result in elevation of inhibitors of mineralization of the skeleton and teeth, principally inorganic pyrophosphate. The impaired skeletal mineralization may result in elevations in serum calcium and phosphate. Clinical features include premature loss of teeth, metatarsal and subtrochanteric fractures as well as fragility fractures. Poor bone healing post fracture has been observed. Myalgias and muscle weakness may also be present. In infancy and childhood, respiratory and neurologic complications can occur.

Conclusions HPP is associated with significant morbidity and mortality. Pharmacologic intervention can result in significant clinical improvement. This Canadian position paper provides an overview of the musculoskeletal, renal, dental, respiratory, and neurologic manifestations of hypophosphatasia. The current state of the art in the diagnosis and management of hypophosphatasia is presented.

Keywords Alkaline phosphatase · Asfotase alfa · Diagnosis · Hypophosphatasia · Management

Introduction and Methods

Hypophosphatasia (HPP) is a rare heterogeneous inherited disorder of bone metabolism [1]. HPP is caused by loss of function mutations in the alkaline phosphatase (*ALPL*) gene with reduction in the activity of the tissue non-specific isoenzyme of alkaline phosphatase (TNSALP) resulting in extracellular accumulation of its endogenous substrates, including inorganic pyrophosphate (PPi) a potent inhibitor of mineralization [2, 3]. TNSALP is expressed in all tissues and is richly expressed in the liver, kidney, and bone [4, 5]. In HPP, inorganic pyrophosphate is not hydrolyzed by alkaline phosphatase (ALP) [2]. Pyridoxal 5′ phosphate (PLP) is the main circulating form of vitamin B_6 and this substrate also accumulates in the presence of loss of function mutations in *ALPL* [6]. Until recently, treatment of HPP was mainly supportive in nature; however, enzyme replacement therapy (ERT) is now available in Canada and the possible indications and contraindications for this option are discussed (Fig. 1).

In this Canadian position paper, national experts reviewed current evidence addressing key questions pertaining to the diagnosis and management of HPP. This paper was supported

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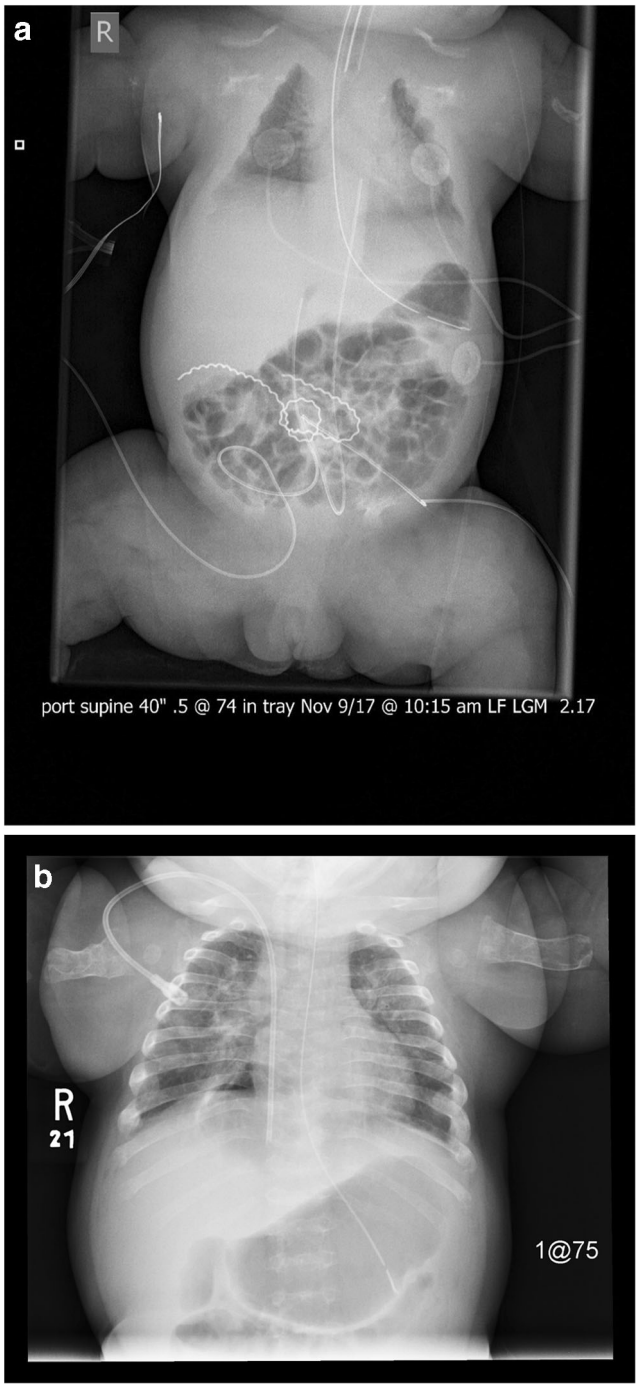

Fig. 1 Dramatic response to enzyme replacement therapy in infant with life/threatening perinatal HPP. Modified skeletal survey at birth (**a**) and after 7 months of enzyme replacement therapy (**b**)

and endorsed by Canadian Endocrine Update, McMaster University (Hamilton), and Western University (London Ontario). We summarize recent advances in diagnosis and treatment of this rare condition and provide recommendations for evaluation and management.

We searched MEDLINE, EMBASE, Cochrane databases from June 1, 2010 to January 30, 2019 using the MeSH search term "hypophosphatasia." We excluded letters, reviews, and editorials and only included English language papers dealing with humans. As evidence is limited, we included all levels of evidence available. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [7] (see Table 1). Papers were identified and reviewed by content expert (AK) and all co-authors contributed to the development of the position paper.

The following questions were addressed:

1. What is the pathophysiology leading to HPP in children and adults?
2. How does HPP present in children and adults and what are the target organ effects?
3. How is HPP diagnosed in children and adults and what is the role of serum alkaline phosphatase, PPi, and DNA sequencing of the ALPL gene?
4. How is HPP treated in children and adults?
5. When should ERT be offered to children and to adults?

What is the pathophysiology leading to HPP in children and adults?

Alkaline phosphatase (ALP) is a hydrolase enzyme (EC 3.1.3.1) discovered by Robert Robison in 1923 [8]. Human alkaline phosphatase (ALP) is encoded by a family of four genes at three different loci. Two loci (*ALPI* and *ALPP*) at 2q37.1 encode three tissue-specific isoenzymes (intestinal [IAP], placental [PLAP], and germ cell [GCAP]) [2, 9]. One locus (*ALPL*) at 1p36.12 encodes the most abundant ALP-called tissue non-specific alkaline phosphatase (TNSALP), and is expressed in the bone, liver, and kidney, and also in the CNS, fibroblasts, and other cell types [4, 5]. These three different genetic loci encode four isoenzymes and are distinct with respect to their posttranslational modifications [6].

TNSALP is a homodimer (composed of two identical subunits) and the monomer to monomer interface is critical for enzymatic stability and function. Three metal binding sites (two occupied by Zn^{++} and one by Mg^{++}) are necessary for enzymatic activity. Another metal binding site is occupied by calcium [3, 10].

TNSALP is a cell surface enzyme attached to the surface of plasma membranes and is anchored there by a glycosylphosphatidylinositol (GPI) moiety [11]. It is biologically active only in a homodimeric form when anchored to the cell membrane. However, TNSALP can also be released into the circulation when the GPI anchor is cleaved by phospholipases also found in the plasma membrane [12, 13].

Although TNSALP can act on a wide variety of substrates in vitro, there are three natural substrates, i.e., PPi, pyridoxal-

Table 1 Quality of evidence assessment criteria

Study design	Quality of evidence	Lower if	Higher if
Randomized trial ➔	High	Risk of bias − 1 serious − 2 very serious	Large effect + 2 very large + 1 large
	Moderate	Inconsistency − 1 serious − 2 very serious	Dose response + 1 evidence of a gradient All plausible confounding
Observational study ➔	Low	Indirectness − 1 serious − 2 very serious	+ 1 would reduce a demonstrated effect or + 1 would suggest a spurious effect when result show no effect
	Very low	Imprecision − 1 serious − 2 very serious	
		Publication bias − 1 likely − 2 very likely	

5′-phosphate (PLP), and phosphoethanolamine (PEA) [14, 15].Two other compounds di-phosphoryl lipopolysaccharide (LPS) and phosphorylated osteopontin (p-OPN) may also be natural substrates [16, 17].

TNSALP accounts for approximately 95% of total serum ALP activity and the so-called bone-specific ALP is its most abundant isoform. Bone-specific ALP is its most abundant form in children. In healthy adults, the bone and liver isoforms of TNSALP are present in approximately equal proportions. TNSALP is present in different cell types, e.g., in pre-osteoblasts, osteoblasts, lining cells, new osteocytes, endosteal cells, bone marrow cells, chondrocytes, cartilage matrix and bone matrix vesicles. In teeth it is expressed in ameloblasts and odontoblasts [18, 19]. TNSALP is not expressed in osteoclasts.

In HPP, rickets or osteomalacia is the consequence of deficiency of TNSALP resulting in defective mineralization of the skeleton and teeth. The processes involved in normal mineralization are complex but the end result is precipitation of calcium and phosphate as hydroxyapatite crystals in collagen fibrils in the extracellular matrix and within matrix vesicles in osteoblasts and chondroblasts [20, 21]. The early phase of mineralization occurs in the matrix vesicles where hydroxyapatite is formed from the calcium and phosphate within the vesicles. The vesicles release their contents including the newly formed hydroxyapatite crystals into the extracellular collagenous matrix [22].

The process is carefully orchestrated by factors that either facilitate or inhibit mineralization. These include three phosphatases, importantly TNSALP but also phosphoethanolamine/phosphocholine phosphatase (PHOSPHO1) which belongs to a superfamily of hydrolases but has phosphatase activity in its active site and nucleotide pyrophosphatase 1 (NPP1). Together, these phosphatases hydrolyze PPi an inhibitor of mineralization, generate PPi, and critically determine the phosphate/PPi ratio [23].

It is thus clear that in HPP, the absence of sufficient TNSALP activity allows the accumulation of PPi. This contributes to the imbalance between minerals and mineralization inhibitors thereby inhibiting the growth of hydroxyapatite crystals and subsequent mineralization [24]. In HPP, the inability to generate phosphate from PPi alters the ratio of phosphate to PPi and inhibits bone mineralization. Nephrocalcinosis may be secondary to elevations in the calcium phosphate product. Also, calcium pyrophosphate crystals deposit in the joints and cause inflammation and crystal arthritis as well as pseudogout. The osteoblasts continue to produce undermineralized bone matrix or osteoid resulting in rickets or osteomalacia which are features of HPP.

The dental problems of HPP share similar pathophysiology with specific issues related to dental biology. There is loss of alveolar bone and enlarged pulp chambers. Cementum mineralization is impaired resulting in loss of primary dentition (deciduous teeth). Impaired dentinogenesis and enamel hypoplasia is also seen [25, 26].

PLP is also dephosphorylated by TNSALP into pyridoxal. PLP is an essential cofactor in neurotransmitter synthesis. Only pyridoxal crosses the blood brain barrier and enters the neuronal cells and is phosphorylated again into PLP. With loss of function mutations in *ALPL* and decrease in TNSALP activity, there is insufficient hydrolysis of PLP with accumulation of the substrate PLP in the circulation and a relative deficiency of pyridoxal in the CNS leading to a defect in Gamma-amino butyric acid (GABA) metabolism in neuronal cells and vitamin B_6—dependent seizures [12–15].

Urine and serum PEA also accumulate in HPP. The biologic consequences of the accumulation of PEA are poorly understood. The effects of accumulation of PEA on muscle function is also not known and requires further evaluation. Its role

in the development of myopathy is not clear and the exact metabolism of PEA is not known at this time [27].

Circulating ALP levels decrease with age and reach adult levels by the age of 13 to 14 in girls and 15 to 17 in boys [28].

HPP follows both autosomal dominant and autosomal recessive patterns of inheritance [6, 27, 29]. The autosomal recessive forms are caused mainly by diverse loss of function missense mutations. This contributes to the variable expression seen in this disorder [29]. Deficient TNSALP activity is caused by autosomal recessive mutations or a single putative dominant-negative mutation in the liver/bone/kidney alkaline phosphatase gene (*ALPL*). Severe forms (perinatal and infantile) are recessively inherited and less severe forms can either result from autosomal dominant or recessive mutations [29]. The prevalence of the severe forms of HPP has been estimated to be 1/300,000 in France and Northern Europe and 1/100,000 in Canada but the prevalence of the milder forms may be much higher. Site-directed mutagenesis studies have also allowed us to classify HPP genetically into "severe recessive" and "mild recessive" and "mild dominant" forms [6]. Genetic counseling can thus be complicated given the 2 modes of inheritance, the marked variability in disease expression, including intrafamilial variation, and the existence of a benign prenatal form that may sometimes be difficult to distinguish from the severe perinatal form. More than 340 mostly missense mutations have been described [6]. The abundance of missense mutations as well as the dominant-negative effect of some mutations leads to the clinical heterogeneity seen in HPP with its very broad range of signs, symptoms and complications. Overall there is some phenotype-genotype correlation, albeit imperfect, suggesting other genetic, epigenetic or environmental factors also modify the phenotype.

Quality of evidence: very low

How does HPP presents in children and adults and what are the target organ effects?

The prevalence of HPP is estimated to be 1 in 100,000 in Canada [30–32]. The Mennonite population in Canada has a much higher prevalence with up to 1 in 2500 being affected [31, 32].

Historically, HPP has traditionally been classified by age at presentation. Pediatric-onset HPP varies significantly in disease severity, even within families. At one end of the spectrum are neonates often diagnosed in utero who present with perinatal disease, in the form of a poorly ossified cranium, compromised length with marked bony deformities and osteochondral spurs. Generalized skeletal hypomineralization is present often with bones that are not visible on X-ray [1]. These neonates are at risk of multisystem disease including increased risk of fracture. Ventilatory support in perinatal HPP is usually required due to severe lung hypoplasia, impaired chest wall mineralization, and muscle weakness. Respiratory failure is the most common cause of death in the perinatal lethal form of HPP [9]. Neurologic features include irritability and seizures due to impaired metabolism of vitamin B_6 [33–35]. The seizures are responsive to high dose pyridoxine vitamin B_6 [36, 37].

The infantile form of HPP also varies in its expression however infants usually present before the age of 6 months with poor feeding, irritability, failure to thrive, weakness and delayed milestones, rachitic radiological abnormalities, and/or craniosynostosis with increased intracranial pressure [38]. Severity is also variable, and there is a risk of respiratory failure within the first year of life. Unlike newborns with perinatal HPP, affected infants may appear normal at birth; however, skeletal demineralization may progress as is the natural history of untreated severe disease.

Untreated, perinatal and infantile HPP have a significant mortality rate resulting from respiratory failure. Survival rates of 42 and 27% at the age of 1 and 5 years, respectively have been reported [39]. In Mennonite babies with perinatal HPP, mortality rates of 100% have been observed [39, 40].

A nonlethal "benign" perinatal form of HPP has also been described and it is critical to differentiate this form, which presents in utero, from classic HPP [41].

In childhood, HPP usually presents after 6 months of age, most often with premature exfoliation of one or more primary teeth. Musculoskeletal (MSK) pain, muscle weakness, and a waddling gait can be significant. While skeletal findings clinically may be subtle, radiologic findings are often noted affecting the long bones. [38].

In childhood HPP, skeletal abnormalities affecting the skull with craniosynostosis and increased intracranial pressure may be seen. Early closure of the cranial sutures is reported in ~20% of individuals with HPP and should be evaluated in any infant or child with signs and symptoms of increased intracranial pressure, seizures or poor head growth, or abnormal skull shape [9]. The premature closure of the cranial sutures can result in increased intracranial pressure and may also pose risks to the optic nerves and spinal cord [42]. TNSALP is involved in the development of the central nervous system, including the proliferation and differentiation of neural stems cells and well as myelination [43, 44]. HPP can be associated with non-specific anxiety, restlessness, and chronic pain [33, 44, 45].

Odontohypophosphatasia (OdontoHPP) is a form of the disease solely characterized by dental symptoms in the absence of skeletal abnormalities [38, 46]. Premature exfoliation of primary teeth is the only physical finding. Odontohypophosphatasia has the same characteristic biochemical findings as systemic HPP; however, they are not as marked as noted in the more severe forms of HPP [29].

Defective mineralization of the periodontal ligament/cementum results in loss of teeth with the root attached, as the tissue necessary to anchor the teeth to alveolar bone is impaired [47]. The first teeth are usually lost by the age of two with the roots intact. The color, shape, and structure of the teeth are abnormal [25, 26, 48–50].

It should be noted that, in the absence of a known family history of HPP, a child presenting with premature loss of deciduous teeth requires further evaluation. The child may have odontoHPP alone and the disease will be limited to the teeth throughout life. This however may also be the presenting feature of childhood HPP or the disease may be dormant and manifest decades later as adult HPP. See Table 2 for a summary of the systemic features of HPP in infants and children.

Adult HPP also has a variable presentation. Surveys completed at the Mayo Clinic suggest that 68% of individuals are symptomatic at presentation with a significant delay between the age of onset of symptoms and diagnosis [51–53]. The Global HPP Registry confirms lengthy delays from the time of presentation of initial symptoms to diagnosis [54]. In another survey of 84 adult patients who had pediatric-onset HPP, often with premature loss of deciduous teeth, 95% experienced pain, 86% had experienced fragility fractures, 62% had muscle weakness, and 60% used gait aids [53]. Adults usually present with stress fractures which are usually metatarsal or subtrochanteric fractures. Individuals with osteomalacia may present with pseudofractures of the femurs. Poor fracture healing is characteristic of HPP. In a recent case series of 19 patients with HPP including 10 patients with adult onset HPP, fractures as well as problems with dentition were the most commonly reported symptoms [55]. However, this may not be noted in all patients. In a recent case series of 19 patients in whom 14 had bone densitometry results available, the BMD (bone mineral density) was either in the low BMD or osteoporosis category. None of the 14 patients had a normal BMD at the lumbar spine and hip [55].

Table 2 Key features of hypophosphatasia which may be present in infants, children, and adults

1. Skeletal manifestations
Decreased bone density with impaired mineralization and osteomalacia
Bowing of the long bones
Fragility fractures with delayed bone healing
Bone pain
Poor bone growth and short stature
Craniosynostosis
2. MSK presentation
Muscle pain
Proximal myopathy
Joint pain
Decreased mobility
Chondrocalcinosis
3. Renal complications
Nephrocalcinosis due to high serum calcium and phosphate
Hypercalciuria
Nephrolithiasis
4. Dental manifestations
Premature loss of primary and secondary teeth
Abnormal color, shape, and structure of teeth
5. Respiratory manifestations
Respiratory failure or insufficiency
6. Neurologic manifestations
Seizures
Anxiety
Restlessness
Chronic pain

The impaired bone mineralization may result in a low BMD on DXA assessment. An incorrect diagnosis of idiopathic osteoporosis may be made in individuals with hypophosphatasia. In this condition, bisphosphonates are contraindicated as bisphosphonates are stable analogs of pyrophosphate and further impair bone mineralization. Denosumab an inhibitor of RANKL and a potent antiresorptive agent may also further decrease bone remodeling and suppress serum ALP further, contributing to impairments in bone mineralization. This requires further evaluation. Atypical femoral fracture may be seen more frequently in individuals with HPP [56–61]. Bone biopsies obtained from the iliac crest in HPP demonstrate the presence of osteomalacia with an increase in non-mineralized osteoid. Calcium pyrophosphate crystals may deposit in the articular cartilage, and in and around the joints, resulting in chondrocalcinosis and pseudogout. Adults may have experienced premature loss of primary and secondary teeth with the root intact [62]. Muscle weakness is often present. The hypercalcemia will contribute to hypercalciuria and elevations in phosphate may also contribute to nephrocalcinosis and subsequent renal insufficiency. Psychologic manifestations include pain, depression, and anxiety [53].

Quality of evidence: very low

How is HPP diagnosed today in children and adults and what is the role of serum alkaline phosphatase, PPi, and DNA sequencing of the ALPL gene?

Being a rare disorder with different modes of presentation, the diagnosis of HPP is often delayed and there is incomplete understanding of its natural history. The diagnosis of HPP is initially suspected by the presence of a low serum alkaline phosphatase. It is important to confirm that the ALP is low and not affected by contamination by EDTA or citrate in the test tube in error [63]. After confirming that the ALP corrected for age and gender is indeed low, other causes of a low ALP

should be excluded [64]. These other causes include any severe illness, major surgery, major trauma, malignancy, or chemotherapy. Individuals with myeloproliferative disorders or individuals who have received massive transfusions may also have low ALP levels. Nutritional deficiencies including protein calorie deficiency, zinc, folate, magnesium, vitamin B_6, or vitamin B_{12} are associated with low ALP levels [64–67]. Antiresorptive therapy and bisphosphonates (and denosumab) as well as vitamin D excess can also result in decreases in ALP levels. Diseases including hypoparathyroidism, hypothyroidism, renal osteodystrophy, achondroplasia, and Wilson's disease, are clinically excluded before confirming a diagnosis of HPP [68, 69]. See Table 3 for summary. The diagnosis of HPP is a clinical diagnosis made on the basis of signs and symptoms of HPP supported by the laboratory findings of a persistently low alkaline phosphatase level. A molecular diagnosis can also be confirmed with DNA sequencing of the alkaline phosphatase gene. PPi measurements are not clinically available. Molecular genetic testing of the *ALPL* gene is not essential to make the diagnosis but is highly recommended as data have accumulated correlating functional testing with clinical phenotype [29]. In addition, elevated PEA is a marker of HPP but shows more variability than PLP.

Quality of evidence: very low

How is HPP treated today in children and adults?

Published case reports evaluating teriparatide in HPP have demonstrated improvements in bone density, bone pain, and in fracture healing [70–73]. Other investigators have not confirmed enhanced fracture healing with teriparatide, and the impact of teriparatide in HPP may depend on the mutation and its severity [74]. Teriparatide use would be considered "off label" as it is not approved for this indication. There have been no controlled clinical trials evaluating teriparatide in HPP. Positive effects with calcitonin have not been observed [75].

Table 3 Causes of low alkaline phosphatase

Drugs
Antiresorptive agents
Vitamin D excess
Chemotherapy
Diseases
Hypoparathyroidism
Hypothyroidism
Renal osteodystrophy
Achondroplasia
Wilson's disease
Myeloma
Miscellaneous
Severe illness
Major surgery or major trauma
Massive transfusions
Nutritional deficiencies (protein, calorie, zinc, folate, magnesium, vitamin B_6, vitamin B_{12})

Enzyme replacement therapy with recombinant tissue nonspecific alkaline phosphatase (TNSALP) is now commercially available for individuals with a confirmed diagnosis of pediatric onset HPP. In 2016, enzyme replacement therapy (ERT) in the form of asfotase alfa was approved by Health Canada for use in patients of any age with pediatric-onset HPP.

Asfotase alfa consists of a recombinant TNSALP homodimer with two identical polypeptide chains each with a catalytic domain linked through a human immunoglobulin IgG_1 Fc fragment to a deca-aspartate tail enabling the molecule to target bone and be retained in bone [76]. Asfotase alfa replaces TNSALP activity at the site of deficiency. This results in reductions in PPi and the availability of phosphate to bind to calcium and form hydroxyapatite. Reductions in PPi restore bone mineralization.

In a phase two, open label study in 11 children under the age of 3 years, asfotase alfa increased circulating TNSALP levels and reduced the substrates PLP and PPi. Bone mineralization dramatically improved as evaluated by the Radiographic Global Impression of Change (RGIC) score and Rickets Severity Scale (RSS) [77]. Pulmonary function, physical function, and development improved [78]. Survival has dramatically improved for babies with perinatal and infantile HPP. The recommended dose is 6 mg/kg of body weight per week and this can be administered as a 1 mg/kg 6 times a week dose or 2 mg/kg 3 times a week dose given subcutaneously. It is of value to rotate the injection site in order to reduce local adverse events. In the perinatal and infantile forms of HPP, treatment with asfotase alfa is life-long. Individual case reports and longer term (5 year) studies have demonstrated improvement in mineralization, respiratory function, and survival rate in 37 patients with perinatal and infantile HPP compared to 48 historical controls [39].

Since the impact of the disease may be reversible, ERT offers the opportunity for a normal life for a previously lethal condition. However, not all babies with perinatal HPP have salvageable disease and treatment failures have been reported [79, 80].

Monitoring guidelines for patients with HPP now treated with ERT have recently been published [81].

Access to treatment is determined by clinical criteria and varies from province to province. Asfotase alfa should be prescribed by specialists in a tertiary care center with expertise in the treatment of severe HPP. Hospitalization for babies with perinatal HPP is prolonged, lasting at least several months. Following discharge ongoing therapy is administered as an outpatient. There is general agreement that children with only the odontoHPP form of the disease are not candidates for ERT.

There is lack of evidence that outcome with respect to adult teeth is improved and there is no evidence that disease progression is prevented for those who develop adult HPP. . Children with odontohypophosphatasia appear to be stable however yearly follow-up is advised to ensure that other systemic features of HPP do not become evident [82]. The value of treating children with HPP who only present with muscle weakness or musculoskeletal pain is currently not confirmed. Children with only muscle weakness or myalgias may subsequently develop fragility fractures later in life and long-term prospective data is required to evaluate the musculoskeletal complications of HPP. The benefits of ERT and duration of therapy if begun in childhood or adolescence requires further long-term prospective study [82]. ERT appears to be reasonably well tolerated.

To date, clinically significant antibody-mediated immune reactions against the recombinant enzyme have not been observed [78]. Common treatment-related adverse reactions include local injection site reactions with mild, localized transient erythema, induration, as well as pruritus. Local injection site pain is reduced by warming the drug to room temperature prior to administration. Local reactions include permanent lipoatrophy or lipohypertrophy as well as changes in skin color [83]. The risk of the local injection site reactions may be reduced by rotating the injection site between the abdomen, deltoid, and thigh [80].

Long-term therapy with asfotase alfa in 13 adults and 6 adolescents with HPP was recently evaluated [83]. The 5-year efficacy and safety of asfotase alfa therapy in adults and adolescents with HPP had as its coprimary efficacy measures reductions in the substrates of TNALP namely PLP and PPi. With asfotase alfa, significant reductions in these substrates were observed [83]. Secondary efficacy measures were evaluation of bone mineralization with bone histomorphometry evaluated at baseline and year 1 in the treated group as well as the control group. Mean osteoid volume decreased with therapy whereas it increased in the control group at month 6. Percent of healthy mean mineralization lag time decreased from baseline to year 1 by a mean (95% CI of − 580% in the asfotase alfa group which was significant ($P < 0.05$). Bone mineral density was measured by DXA and no statistically significant differences between treated and control patients were observed during this time period. Clinical improvement was documented with improved walking ability which increased significantly at month 6 and years 1, 2, and 3 ($P < 0.05$) Muscle strength and running speed improved with asfotase alfa therapy in comparison to controls [83]. Five of the 19 patients required gait aids during the 6-min walk test at baseline, and demonstrated improvements in gait and balance with a reduction in the use of gait aids with therapy. The treatment was well tolerated. Adverse reactions included injection site reactions and lipodystrophy or hypertrophy as well as local skin discoloration [83].

Five Canadian adult HPP patients who participated in the 6-year clinical trials of ERT and did not continue on therapy at the end of the study period experienced significant deterioration in gross motor function, with reappearance of severe pain. They required mobility devices which had previously been discontinued with therapy during the clinical trial. New poorly healing fractures occurred in 3/5 patients with reductions in quality of life (QOL). Mobility also declined in all five patients following 1 year of cessation of ERT. All patients were subsequently restarted on asfotase alfa with significant improvement in function and QOL (personal communication CRG, unpublished data).

Quality of evidence: moderate

When should enzyme replacement therapy be offered to children and to adults?

Currently, ERT is approved in Canada for patients of all ages with pediatric-onset HPP who meet clinical criteria for treatment.

These Canadian recommendations advise that adults with HPP be considered for treatment with ERT in the presence of the following criteria:

1. Osteomalacia and complications of osteomalacia
2. Pseudofractures.
3. Intractable musculoskeletal pain requiring or unresponsive to opioids.
4. Presence of chondrocalcinosis with intractable pain
5. Major osteoporotic fractures.
6. Delayed or incomplete fracture healing.
7. Individuals with significant impairment in function with impaired gait and mobility.

Prior to proceeding with ERT, a confirmed diagnosis of HPP is required with identification of the goals of therapy. As osteoporosis is common, a bone biopsy may be of value to confirm the presence of osteomalacia prior to proceeding with ERT in adults. If a bone biopsy is completed, it is essential to ensure appropriate tetracycline labelling is completed and perform histomorphometery on non-decalcified specimens. Further study and long-term data in adults will be of value in determining the indications for treatment with ERT and the ideal duration of therapy.

Conclusion

In summary, HPP is a rare inherited disorder of bone and mineral metabolism. It is caused by loss of function mutations in the ALPL gene. Extreme variability in the presentation of this condition is noted in children and adults and natural

history (particularly in adolescents and adults) is poorly understood. The diagnosis is often missed or delayed in children, and in particular in adults, and it is essential to emphasize the need for evaluation of an abnormally low serum ALP level. Enzyme replacement therapy for HPP is now available. We have provided an overview of the Canadian status with respect to ERT and current Canadian recommendations for the management of HPP with ERT. This is a rapidly evolving field and more detailed recommendations will be developed with the availability of new clinical evidence regarding management options in hypophosphatasia.

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Compliance with ethical standards

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