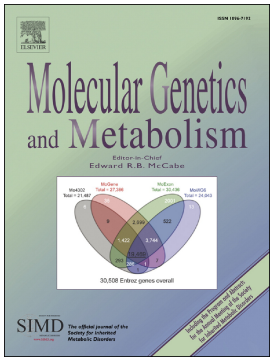

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Monitoring Guidance for Patients With Hypophosphatasia Treated With Asfotase Alfa

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Disclaimer: These consensus recommendations are based on the expert opinion of an international panel of physicians experienced in the management of hypophosphatasia. Adherence to these recommendations is completely voluntary. These recommendations are intended to serve as a basic framework for monitoring patients with hypophosphatasia for whom the decision to treat has been made. Ultimately, the treatment and monitoring of patients with hypophosphatasia should be tailored to the patient based on the individual's clinical manifestations, medical history, and the clinician's professional judgment. Clinicians are advised that the recommendations provided may evolve as more scientific information becomes available.

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Running head: Monitoring Patients Treated With Asfotase Alfa

ABSTRACT

Hypophosphatasia (HPP) is a rare, inherited, systemic, metabolic disorder caused by autosomal recessive mutations or a single dominant-negative mutation in the gene encoding tissue-nonspecific alkaline phosphatase (TNSALP). The disease is associated with a broad range of signs, symptoms, and complications, including impaired skeletal mineralization, altered calcium and phosphate metabolism, recurrent fractures, pain, respiratory problems, impaired growth and mobility, premature tooth loss, developmental delay, and seizures. Asfotase alfa is a human, recombinant enzyme replacement therapy that is approved in many countries for the treatment of patients with HPP. To address the unmet need for guidance in the monitoring of patients receiving asfotase alfa, an international panel of physicians with experience in diagnosing and managing HPP convened in May 2016 to discuss treatment monitoring parameters. The panel discussions focused on recommendations for assessing and monitoring patients after the decision to treat with asfotase alfa had been made and did not include recommendations for whom to treat. Based on the consensus of panel members, this review provides guidance on the monitoring of patients with HPP during treatment with asfotase alfa, including recommendations for laboratory, efficacy, and safety assessments and the frequency with which these should be performed during the course of treatment. Recommended assessments are based on patient age and include regular monitoring of biochemistry, skeletal radiographs, respiratory function, growth, pain, mobility and motor function, and quality of life. Because of the systemic presentation of HPP, a coordinated, multidisciplinary, team-based, patient-focused approach is recommended in the management of patients receiving asfotase alfa.

Monitoring of efficacy and safety outcomes must be tailored to the individual patient, depending on medical history, clinical manifestations, availability of resources in the clinical setting, and the clinician's professional judgment.

Keywords: Enzyme replacement therapy; alkaline phosphatase; tissue-nonspecific alkaline phosphatase; asfotase alfa; hypophosphatasia; metabolic bone diseases; therapeutic drug monitoring.

Highlights

- Asfotase alfa is an enzyme replacement therapy for treatment of hypophosphatasia
- Parameters that should be monitored during treatment with asfotase alfa are reviewed
- A coordinated, multidisciplinary, patient-focused approach is recommended

INTRODUCTION

Hypophosphatasia (HPP) is a rare, inherited, systemic, metabolic disorder that is sometimes life-threatening in infants and can lead to disability at any age. HPP is characterized by low activity of the enzyme tissue-nonspecific alkaline phosphatase (TNSALP), resulting in a broad range of signs, symptoms, and complications (1, 2). Deficient TNSALP activity in HPP is caused by autosomal recessive mutations or a single putative dominant-negative mutation in the liver/bone/kidney alkaline phosphatase (ALP) gene (*ALPL*) encoding TNSALP (3, 4) and leads to extracellular accumulation of TNSALP substrates, chiefly inorganic pyrophosphate (PPi; an inhibitor of hydroxyapatite crystal formation and bone mineralization) (2, 5, 6) and pyridoxal-5'-phosphate (PLP; the circulating form of vitamin B_6, which without TNSALP activity is thought to fail to cross the blood-brain barrier, as well as cell membranes) (2, 7, 8). Phosphoethanolamine (PEA; a degradation product of cell surface phosphatidylinositol-glycan anchors) is also a substrate, although not exclusively, of TNSALP in vitro (9-11).

Depending on the patient's age, the signs, symptoms, and complications of HPP can include bone anomalies detected in utero; premature tooth loss (exfoliation of the entire tooth including root); impaired skeletal mineralization; bone deformities; fractures; bone/joint/muscle pain; respiratory compromise that may require ventilation; impaired growth and mobility; vitamin B_6-dependent seizures; craniosynostosis; substantial morbidity; and, in some cases, death (2, 12, 13).

The clinical presentation of HPP is possibly influenced by autosomal dominant versus autosomal recessive inheritance (14, 15), as well as environmental and epigenetic factors and modifier genes (16). HPP has been clinically classified according to age at first sign or symptom onset: perinatal (in utero and at birth), infantile (age <6 months), childhood (age ≥6 months to <18 years), and adult (age ≥18 years) (1, 2, 15, 17). HPP presenting primarily with dental manifestations has been described as odontohypophosphatasia (18-20). Skeletal manifestations of HPP in utero have been observed, which in some cases may resolve spontaneously after birth; this has been described as benign prenatal HPP (21, 22). These categories are helpful in describing the disease; however, the clinical presentation of HPP is variable (23) and the disease burden throughout an individual patient's life is not well understood (12, 14, 24). Substantial morbidities may develop during the lifetime of a patient with HPP (25), who may have increasing disease burden resulting from joint problems, fractures, orthopedic/dental surgeries, pain, muscular insufficiency, decreased functional status, and impaired mobility (1, 25, 26).

Until recently, treatment of HPP consisted largely of supportive care (2). Use of bisphosphonates has not been rigorously studied in patients with HPP (27); in case studies of adults with previously undiagnosed HPP, treatment with bisphosphonates potentially led to an increase in and/or worsening of fractures (28, 29). Teriparatide (recombinant human parathyroid hormone [PTH] 1–34) has shown some benefit in case studies of adults with HPP (30, 31), although one case report described no benefit (32). Teriparatide is contraindicated in pediatric and young adult patients with open

epiphyses; studies in rats showed an increase in the incidence of osteosarcoma that was dose and treatment duration dependent (27, 33). Teriparatide is currently not recommended for use in the treatment of osteoporosis for longer than 2 years over a lifetime (33). Case reports for other approaches such as bone marrow and stem cell transplantation in infants and children with HPP have reported some improvement in skeletal mineralization and survival to at least age 3 to 7 years in patients with life-threatening disease; however, the improvement in skeletal mineralization was not necessarily associated with an improvement in ALP activity (34-36).

Asfotase alfa (Strensiq®; Alexion Pharmaceuticals, Inc., New Haven, CT, USA), a human, recombinant TNSALP replacement therapy, replaces deficient TNSALP activity in patients with HPP and reduces the accumulation of extracellular TNSALP substrates (37). The efficacy and safety of asfotase alfa was assessed in 5 prospective, open-label, Phase 2, multinational clinical studies in infants and adolescents with perinatal, infantile, or childhood HPP (37-40). In these studies, asfotase alfa improved bone mineralization based on radiographic and biopsy findings and improved growth, respiratory function, and mobility. A study of asfotase alfa in adolescents and adults with HPP has been completed, and the results are being prepared for publication.

No published guidelines are available for monitoring patients with HPP being treated with asfotase alfa. To address this unmet need, in May 2016, Alexion Pharmaceuticals, Inc., convened an international panel of physicians to discuss treatment monitoring parameters for patients with HPP who are receiving asfotase alfa. For this discussion, it

was presumed that the decision to treat with asfotase alfa had already been made; other possible therapeutic approaches, symptom management with other treatments, and general management of HPP were not discussed and are beyond the scope of this report. It should also be noted that access to and experience with this drug currently vary from country to country. Further, the decision to discontinue treatment is complex and beyond the scope of this paper; the decision is multifactorial and should be considered using a case-by-case approach based on discussions and understanding between the patient, family, and physicians. The intention of this consensus report is to provide guidance on the monitoring of patients with HPP receiving treatment with asfotase alfa, including clinical recommendations concerning laboratory, efficacy, and safety assessments and the frequency with which these may be performed during the course of treatment.

Methodology

All physicians involved in the panel discussions were experienced in the management of HPP. Their areas of expertise included pediatrics, metabolic bone disease, endocrinology, gastroenterology, genetics, clinical biochemistry, and orthopedic surgery. After the meeting, nurses experienced in administering asfotase alfa were consulted to obtain feedback on their recommendations for injection technique.

During the meeting, panel members reached consensus on the monitoring of infants, children, and adults with HPP treated with asfotase alfa and prioritized the importance of assessments for each age group. Evidence from the asfotase alfa clinical studies was

used where available and appropriate to guide recommendations. A comprehensive review of the literature was undertaken to establish the foundation for diagnosis and genetic testing of HPP. All authors reviewed and unanimously approved these recommendations.

Although these recommendations provide a basic framework, the signs, symptoms, and complications of HPP vary widely from patient to patient. Thus, treatment and monitoring ultimately should be tailored to the patient based on the individual's medical history, clinical manifestations, and the clinician's professional judgment.

Diagnosis

Considerations for the diagnosis of HPP have been reviewed in other publications (1, 12) and were not a primary focus of the panel discussions. Briefly, the diagnosis of HPP in patients of any age can be established based on characteristic signs, symptoms, and complications of HPP (**Table 1**) (1, 2, 9, 13, 26, 39, 41-52) in combination with consistently low age- and sex-adjusted serum ALP activity (1, 13) after exclusion of other causes of low ALP activity and skeletal diseases with similar presentations (2). Because the lower limit of normal for ALP activity varies by age and sex (53), measured activity must be compared with the lower limit and range appropriate for the patient (13). Physicians should be aware that many institutions do not routinely flag low ALP activity (2) and may incorrectly use adult ALP reference ranges and apply them to patients of all ages. It should be emphasized that age- and sex-adjusted ALP reference intervals are critical to making an accurate diagnosis of HPP. Obtaining activity of the bone isoform

of ALP is generally not necessary or helpful, although it too would be expected to be low compared with age- and sex-adjustedreference intervals. Additionally, elevated concentrations of ALP substrates, including plasma PPi, plasma PLP, and urine PEA, may help support the diagnosis for all age groups (2, 24, 54), although elevation of natural substrates may vary by patient (55-58).

Table 1. Clinical, biochemical, and radiologic features of HPP* (1, 2, 9, 13, 26, 39, 41-52)

Perinatal/Infantile (In utero to <6 months of age)	**Childhood** (≥6 months to 18 years of age)	**Adult** (≥18 years of age)
• Stillbirth • Respiratory failure or insufficiency requiring support • Severe chest deformity (rachitic chest, gracile ribs, rib fractures, narrow thoracic inlet) • Severe skeletal hypomineralization or undermineralization • Osteochondral spurs • Rachitic-like lesions • Metaphyseal radiolucencies • Bowing deformities with or without fractures • Limb shortening • Muscle weakness with hypotonia • Intracranial hemorrhages • Seizures (vitamin B_6 dependent) • Craniosynostosis leading to raised intracranial pressure	• Poor bone mineralization • Bowing deformity • Rachitic-like lesions • Metaphyseal radiolucencies • Fractures • Delayed walking • Waddling gait • Muscle weakness • Missed motor milestones • Pain and stiffness • Short stature • Craniosynostosis leading to raised intracranial pressure • Hearing loss • Failure to thrive • Hypercalciuria • Nephrocalcinosis • Ophthalmic calcifications • Premature loss of teeth with intact	• Poorly healing or recurrent fractures (metatarsal stress, subtrochanteric femoral pseudo-fractures) • Joint dislocation • Chronic muscle or bone pain • Muscle weakness • Fatigue • Immobility • Osteoarthropathy • Osteomalacia • Pseudogout/calcium pyrophosphate deposition disease/crystal arthropathy • Chondrocalcinosis • Nephrocalcinosis • Risk for ophthalmic calcifications • Adult tooth loss • Abnormal dentition, including discoloration, excessive dental caries, use of bridges/loose teeth

Perinatal/Infantile (In utero to <6 months of age)	**Childhood** (≥6 months to 18 years of age)	**Adult** (≥18 years of age)
• Hearing loss • Failure to thrive • Hypercalciuria • Nephrocalcinosis • Ophthalmic calcifications • Premature deciduous tooth loss	roots/lack of cementum	• Premature loss of teeth with intact roots/lack of cementum

*These categories are helpful in describing the disease; however, the clinical presentation of HPP is variable and the disease burden throughout an individual patient's life is not well understood.

HPP, hypophosphatasia.

Genetic testing

More than 330 distinct mutations in the *ALPL* gene encoding the TNSALP enzyme in HPP have been identified (4, 59, 60). Genetic testing for TNSALP mutations is helpful as a confirmatory tool in cases of diagnostic uncertainty, to counsel the family on the risk of inheritance for other family members and to advance understanding of the disease (61). Involvement of a clinical geneticist in the interpretation of these results is warranted. The recommended initial test is *ALPL*-gene sequencing, and if results are normal, it is recommended to proceed to deletion/duplication analysis. In clinical practice, it is common to order both simultaneously, with instructions to "reflex" to deletion/duplication if sequencing to improve convenience for the patient and ordering provider. Sequencing of the *ALPL* gene by Sanger sequencing or next generation sequencing should include all exons and should extend into splice site regions. To date, this allows for detection of approximately 95% of the known *ALPL* mutations (59, 60). Multigene panels that include *ALPL* may also be used, particularly in cases of diagnostic uncertainty. Ordering clinicians should be aware of the depth of coverage when using next generation sequencing technology or whole-exome sequencing, as low coverage regions may harbor pathogenic variants that are not detected. Recommendations for genetic testing will change as research advances.

MULTIDISCIPLINARY MANAGEMENT OF PATIENTS WITH HPP

Given the heterogeneity of HPP, patients may present to a number of different healthcare professionals. A coordinated, team-based approach is essential to the effective management of a patient with this disease, regardless of chosen therapy or

management approach. The multidisciplinary team should include an individual who will serve as coordinator of care in charge of managing the disease and a core care team (**Figure 1**). The core care team would be frequently engaged in managing various aspects of patient care and change as the patient ages, whereas specialists would vary more by presentation. For infants and children with HPP, it is recommended that the core care team include an endocrinologist, medical geneticist, pediatrician, or other healthcare professional specializing in pediatric metabolic bone disorders to be responsible for coordinating care and overseeing the challenges of managing patients with HPP. As children with HPP become adults and require different services, new treatment teams with expertise in musculoskeletal disorders/disabilities and metabolic diseases will need to be established. Coordination of care may vary by country, region, center, and available resources. Dentists, nurses and allied health professionals (e.g., social workers, genetic counselors, physical therapists, occupational therapists) experienced in HPP may also play an important role in patient education and family support.

Figure 1.

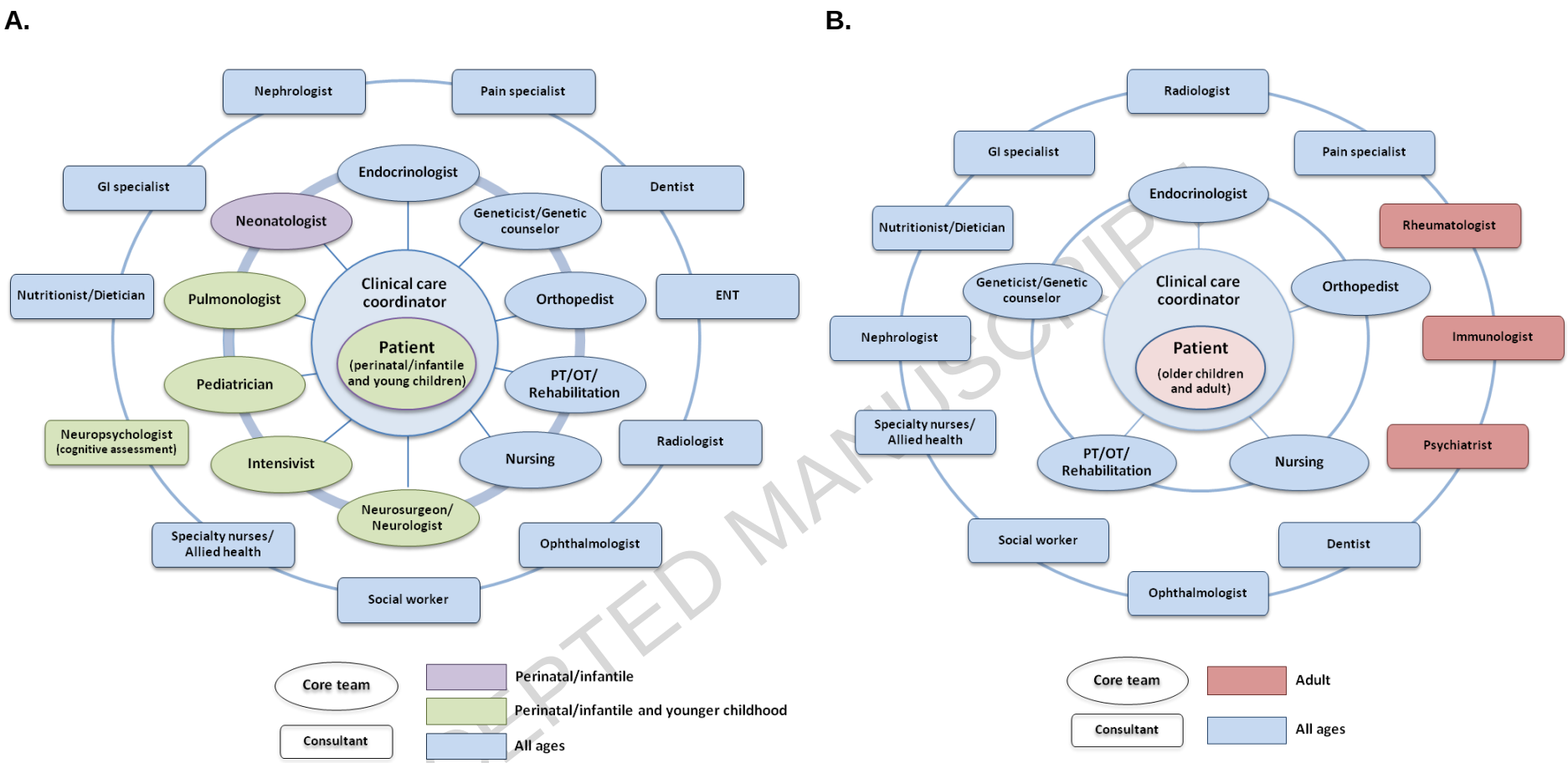


Figure 1. Multidisciplinary care team considerations for monitoring (**A**) perinatal patients, infants, and younger children with HPP and (**B**) older children and adults with HPP. Members of the core care team are represented by the oval shapes in the inner circle. Consultants are represented by the rectangles in the outer circle. Note a gradual transition of members of the core care team as the patient ages from a younger child to an older child and adult. This configuration of specialists can vary based on individual patient, country in which they are treated, and regional medical practices.

ENT, ear, nose, and throat specialist; GI, gastrointestinal; HPP, hypophosphatasia; OT, occupational therapist; PT, physical therapist.

TREATMENT GOALS

The goals of treatment with asfotase alfa in patients with HPP are presented in **Table 2** and focus on attainment of good health and function. For perinatal/infantile patients, goals include survival, improved ventilatory status, control of seizures, and discharge from hospital. Treatment of infants and children with HPP has similar goals, such as improved growth and mobility (depending on initial clinical presentation), improved neurologic development, and improved mineralization of bone. For adult patients with fractures, treatment goals include reduced number and frequency of fractures, particularly pseudo-fractures and insufficiency fractures, and improved fracture healing; it is also important to avoid treatments that could cause further clinical deterioration (e.g., bisphosphonates). In adults with and without fractures, goals include improved functional status as measured by strength, endurance, and improvements in gait. Reducing fatigue is also an important treatment goal, given that fatigue may be a considerable cause of morbidity in adults with HPP. Important goals for all patients include oral health, meeting developmental milestones, improvements in mobility, reduced pain, and improved quality of life (QOL).

Table 2. Treatment goals for patients with HPP treated with asfotase alfa

Perinatal/Infantile (In utero to <6 months of age)	**Childhood** (≥6 months to 18 years of age)	**Adult** (≥18 years of age)

• Survival
• Improved respiratory status (ventilatory support)
• Skeletal improvements
• Metabolic control, prevention of renal failure
• Improved growth and physical development (e.g., weight gain)
• Meet developmental milestones
• Treat craniosynostosis
• Seizure control
• Hospital discharge
• Pain reduction
• Oral health
• Improved quality of life
	• Improved mobility
	• Skeletal improvements
	• Radiographic improvements (reduced tongues of radiolucency)
	• Improved growth
	• Meet developmental milestones
	• Nephrocalcinosis prevention
	• Pain reduction
	• Oral health
	• Improved quality of life
		• Patients with fractures
		  ○ Improved fracture healing
		  ○ Reduced fracture frequency
		  ○ Reduced number/prevention of pseudo-fractures and insufficiency fractures
		  ○ Avoidance of treatments that could cause further clinical deterioration (e.g., bisphosphonates)
		• Patients with and without fractures*
		  ○ Improved functional status
		  – Endurance
		  – Strength
		  – Gait/walking
		  ○ Reduced fatigue
		  ○ Reduced dislocations
		  ○ Improved joint issues
		  ○ Reduced joint pain
		  ○ Improved bone quality
		  ○ Pain reduction

Perinatal/Infantile (In utero to <6 months of age)	**Childhood** (≥6 months to 18 years of age)	**Adult** (≥18 years of age)
		○ Oral health ○ Improved quality of life

*Patients may have residual complications owing to past fractures.

HPP, hypophosphatasia.

MONITORING RECOMMENDATIONS

Members of the advisory panel reached consensus on recommendations for laboratory, efficacy, and safety assessments and their frequency in the monitoring of patients with HPP who are treated with asfotase alfa. Recommendations vary by age group and are summarized below for infants, children, and adults with HPP.

Laboratory testing

Recommendations for laboratory monitoring are summarized for all age groups in **Table 3**. Measurement of ALP activity (adjusted for age and sex) is critical for the diagnosis of HPP and is an essential minimum baseline assessment for all patients treated with asfotase alfa. After treatment initiation, monitoring ALP activity may be useful in discussions about medication compliance with patients, parents, or caregivers and potentially provide insights on immune responses (e.g., if a patient has continued increases in ALP activity but no clinical improvement, this could be because of neutralizing antibodies).

Table 3. Laboratory assessments in patients with HPP treated with asfotase alfa

Laboratory Test	Frequency	Special Considerations
ALP activity	• Perinatal/infantile: Baseline, 3, 6, and 12 mo, and then every 6 mo • Childhood and adult: Baseline, 2 wk, 3, 6, and 12 mo, and then annually	• Critical for diagnosis • Ensure that testing lab uses age and gender-adjusted reference ranges • Significant changes may require further investigation • May be useful in assessing compliance • Note on test request form that the sample should be diluted if possible to get an accurate reading
Plasma PLP	• Perinatal/infantile: Baseline, 1, 3, 6, and 12 mo, and then annually • Childhood and adult: Baseline, 3 mo, and then annually	• Active form of vitamin B_6 • Vitamin B_6 supplements can confound results • Current issues with testing while on asfotase alfa owing to degradation in vial would necessitate addition of an ALP inhibitor, such as levamisole, to the vial for results to be interpretable
Plasma PPi	• PPi levels were measured in the clinical trial program for asfotase alfa. Reductions were observed within 6–12 wk of treatment; however, reductions were not correlated with clinical outcomes. The clinical utility of this assessment has not been explored in the real-world setting	• Not commercially available

Laboratory Test	Frequency	Special Considerations
Urine PEA	• Perinatal/infantile: Baseline, 1, 3, 6, and 12 mo, and then annually • Childhood and adult: Baseline, 3 mo, and then annually	• Can support diagnosis
Calcium	• Perinatal/infantile: Baseline, 1, 3, 6, and 12 mo, then annually; monitor as needed in the acute hypercalcemic until controlled • Childhood and adult: Baseline, 3 mo, and then annually	• Serum calcium should be adjusted for albumin • Ionized calcium (preferred, most consistent) • Hypercalcemia may be evident at diagnosis • Hypocalcemia may occur on treatment; supplementation may be needed when on asfotase alfa • Assess more frequently if patient is not improving on treatment • Calcium abnormalities are rare in adults, but may be in the upper limits of the reference range • Can be done locally and can be available at appointments
PTH	• Baseline and then periodically based on calcium metabolism in individual patient	• For detecting alterations in bone/mineral metabolism • Related to long-term calcium levels • Perform if calcium levels present an issue • Can be done locally and can be available at appointments

Laboratory Test	Frequency	Special Considerations
Vitamin D (25-hydroxyvitamin D)	• Perinatal/infantile: Baseline, 1, 3, 6, and 12 mo, and then annually once normal levels reached • Childhood and adult: Baseline, 3, 6, and 12 mo, and then annually once normal levels reached	• For ruling out additional cause of deficient mineralization • Ensure vitamin D sufficiency during treatment • Patients with confirmed deficiency should receive supplementation and be reassessed periodically • Can be done locally and can be available at appointments
PO_4	• Perinatal/infantile: Baseline, 1, 3, 6, and 12 mo, and then annually • Childhood and adult: Baseline, 3 mo, and then annually	• Monitor for serum phosphate (In clinical trials, initial changes in serum phosphate levels were variable in response to treatment, with some patients experiencing an increase and some a decrease, but the values normalized with continued treatment. Some decreases in serum phosphate levels appeared to coincide with decreases in serum calcium during the first several weeks of treatment, likely due to increased skeletal mineralization) • Assess more frequently if patient is not improving on treatment. • Can be done locally and can be available at appointments

Laboratory Test	Frequency	Special Considerations
Routine blood tests	• Perinatal/infantile: Baseline, 3, 6, 9, and 12 mo, and then annually – Monitor closely during acute phase until stable • Childhood and adult: Baseline, 6 mo, and then annually	• Complete blood count • Liver function (bilirubin, ALT, AST) • Electrolytes
Classic renal panel	• Perinatal/infantile: Baseline and every 3 mo – Monitor closely during acute phase until stable • Childhood and adult: Baseline, 6 mo, and then annually	• Creatinine, BUN • eGFR (adults) • Urine Ca/Cr (monitor for nephrocalcinosis)
ADA (anti-asfotase alfa IgG)	• All groups: As clinically indicated and available	• Not commercially available • Currently available for research use onlyand through the HPP registry (www.hppregistry.com) • Ideally, test will include information on whether ADA are neutralizing • Interpretation of results and impact on patient management remain to be determined

ADA, antidrug antibodies; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca/Cr, calcium/creatinine ratio; eGFR, estimated glomerular filtration rate; HPP, hypophosphatasia; IgG, immunoglobulin G; PEA, phosphoethanolamine; PLP, pyridoxal-5'-phosphate; PPi, inorganic pyrophosphate; PTH, parathyroid hormone.

At this time, laboratory testing for PPi is not commercially available and has been performed only in the research setting (2); the availability of this assay may increase in the future. Concentrations of plasma PLP may be assessed by measuring vitamin B_6, and urinary PEA can be measured using commercially available tests, such as urine amino acids.

Assay consistency should be considered when interpreting biochemical test results (e.g., fasting conditions in children and adults, discontinuing supplements 1 week before testing, if possible). As expected, in clinical studies, administration of asfotase alfa resulted in measurements of serum ALP activity above the normal range (up to several thousand units per liter). Substrates of TNSALP (PPi, PLP, and PEA) are commonly high in patients with HPP and are often used to support diagnosis. However, it is not unusual for concentrations of PPi and PLP to be undetectable in patients treated with asfotase alfa as an artifact of asfotase alfa continuing to hydrolyze substrates in blood collection tubes during processing. To accurately measure PPi and PLP concentrations, an ALP inhibitor, such as levamisole, would need to be added to blood samples to inhibit in vitro degradation of PPi and PLP to allow for correct interpretation of the results and to guide treatment.

Asfotase alfa may interact with enzyme-linked immunosorbent assays (ELISAs) that use ALP as the enzyme conjugate for quantification. Depending on the design of the ELISA, the presence of asfotase alfa may cause false lows in some tests and false highs in others. Because of this potential for interference, use of assays that do not include an

ALP conjugate is recommended for patients treated with asfotase alfa. Laboratories and clinicians are encouraged to liaise closely with their clinical chemist or pathology department if a patient receiving treatment with asfotase alfa has laboratory test results that seem unusual.

Perinatal and infantile patients

Perinatal and infantile patients with HPP are very fragile and usually require treatment in an intensive care setting. A schedule of assessments recommended for monitoring perinatal and infantile patients is summarized in **Table 4**. Radiographs reviewed by a radiologist familiar with HPP are critical for diagnosis and monitoring response to treatment in these patients. At baseline, a comprehensive skeletal survey should be performed. Some patients may show skeletal improvement as early as 1 month after treatment initiation; however, the panel's consensus was to obtain radiographs of the chest, wrists, and knees 3, 6, and 12 months after initiating asfotase alfa, except when disease severity warrants more frequent imaging. Radiographic findings after 6 months of treatment can help guide decisions regarding dose adjustments; more frequent radiographic assessments should be limited to minimize radiation exposure, unless clinically indicated. Baseline respiratory assessments and age-appropriate pulmonary function testing are recommended, with more frequent monitoring and/or respiratory consults based on individual patient symptoms. Even a patient that is off a ventilator may experience persistent respiratory compromise.

Table 4. Monitoring recommendations for perinatal/infantile patients with HPP treated with asfotase alfa

Assessment	Frequency	Special Considerations
Radiograph	Baseline, 3, 6, and 12 mo, and then annually for wrists and every 2 y for knees, or as clinically indicated	• Critical for diagnosis • Comprehensive skeletal survey* • Radiographs of knees, wrists, and chest used to monitor treatment • Consider dose adjustment after 6 mo on treatment with no improvement and if no other causes of drug failure identified • Study data support 3 mo on assessment schedule
Respiratory	Baseline and then as clinically indicated	• Extremely important assessment/consultation for this age group • Mode of ventilation: Room air O_2 saturation, noninvasive ventilation, CPAP, BiPAP, ventilator, tracheostomy • Sleep study before discharge and per pulmonary consultation until normal • Pulmonary consultation before air flight—consider hypoxia altitude simulation test
Growth	Baseline, every 3 mo until age 4, and then every 6 mo	• Length (before 2 y), height (after 2 y), weight, and head circumference • Should be performed routinely by primary care physician
Motor function	Baseline, 3, 6 and 12 mo, and then annually	• To be performed by PT/OT (Bayley Scales of Infant Development recommended (62)) • AIMS (63) and GMFM (64) can also be used • Gauge changes through informal discussions during appointments
Pain	Baseline, every mo for the first 6 mo, and then every 3 mo	• Monitor with every visit • Consider a tool such as NIPS (65)

Assessment	Frequency	Special Considerations
QOL	Baseline and then annually	• May be challenging to assess; consider a tool such as the PedsQL Infant Scales (66) or EQ-5D-5L (2-page survey for parents) (67)
Safety	See **Table 8**	

*Anteroposterior projections of the left wrist can be used to monitor epiphyses involvement and bone age in pediatric through adolescent HPP patients and may be obtained annually. A skeletal survey for HPP may additionally include anteroposterior projections of feet (focus metatarsals), tibia/fibula and femur (including femoral head), chest, spine (include lateral), and skull (include lateral). With growth and closing of epiphyses, films focused more on known problem areas in a specific individual are more useful than a complete survey. Screening for potential progression or general complication (e.g., kyphoscoliosis, chondrocalcinosis, bone mineral loss) or age-dependent complications (e.g., craniosynostosis in children, occult metatarsal stress fractures in adults) should ensue as patients get older.

AIMS, Alberta Infant Motor Scale; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; EQ-5D-5L, EuroQol 5-dimension 5-level health questionnaire; GMFM, Gross Motor Function Measure; HPP, hypophosphatasia; NIPS, Neonatal Infant Pain Scale; OT, occupational therapist; PedsQL, Pediatric Quality of Life Inventory; PT, physical therapist; QOL, quality of life.

Growth parameters should be routinely monitored and include length/height, weight, body mass index, and head circumference and shape (failure of the skull to grow can indicate craniosynostosis); on treatment, these parameters may be maintained, increase, or in some cases, exceed percentile lines. Routine monitoring of gross and fine motor function by a physical therapist and occupational therapist is recommended for patients of all ages. Baseline and follow-up assessments of pain and QOL are also important but difficult to assess in perinatal and infantile patients because no HPP-specific tool exists to evaluate these parameters. Until such tools become available, the Neonatal Infant Pain Scale (65, 68) may be used to monitor pain and the PedsQL™ (Pediatric Quality of Life Inventory) Infant Scales (66) may be used to monitor QOL.

Children

A schedule of recommended assessments for monitoring children with HPP is summarized in **Table 5**. Given the variability of clinical manifestations in children and the wide age range of patients (6 months to <18 years), the panel divided the group by age and discussed differences in treatment monitoring for younger (6 months to <5 years at first signs or symptoms) versus older (≥5 to <18 years at first signs or symptoms) children. At baseline, respiratory assessments and pulmonary function testing are important for both younger and older children; more frequent monitoring and/or respiratory consults may be considered based on individual patient symptoms. If sleep studies show sleep disordered breathing, assessment by an ear, nose, and throat specialist and/or pulmonologist may be necessary (69). Dental assessments are important after teeth have erupted. Baseline assessment of bone mineral density (BMD)

using dual-energy X-ray absorptiometry (DXA; height-adjusted lumbar spine and total body) may be useful (see *Adults* section), although use of DXA in HPP patients can be confounded by aberrant density readings, which we speculate may be a result of increased proteinaceous components of nonmineralized bones; its use warrants further research. Further recommendations on the use of DXA in children are provided by the International Society for Clinical Densitometry (70).

Table 5. Monitoring recommendations for children with HPP treated with asfotase alfa

Assessment	Frequency	Special Considerations
Radiograph	Baseline, 6 and 12 mo, and then annually for wrists and every 2 y for knees, or as clinically indicated	• Comprehensive skeletal survey at diagnosis as appropriate • Bilateral wrist/knee for monitoring treatment • Use of RSS is recommended to follow improvement of rachitic changes
DXA	At physician's discretion; at least every 2 y	• Normalized data are not available for children aged <3 y, but absolute BMD values can be used to measure change over time
Respiratory	Baseline and then as clinically indicated	• ENT assessment for older children (aged ≥5 y at first symptoms) for concerns regarding upper airway obstruction • Pulmonary function test for concerns regarding lower airway or pulmonary function • Level of respiratory support important at baseline • Annually in patients with bronchomalacia or laryngomalacia
Dental	Baseline; normal dental care	• Only after teeth have erupted
Growth	Baseline, every 3 mo until age 4, and then every 6 mo	• Length, height, weight, and head circumference • Should be performed routinely by primary care physician
Motor milestones	Routine baseline, and then every 6 mo	• To be performed by PT/OT (Bayley Scales of Infant Development (62) or Peabody Developmental Motor Scales (71) recommended, based on age
Mobility	Baseline, at 3 mo, and then once a year	• 6MWT (for ambulatory children aged ≥5 y) (72) • Alberta Infant Motor Scale (63) and Gross Motor Function Measure (64) are recommended for younger children

Assessment	Frequency	Special Considerations
		• If available, record video for comparisons over time
Gait	Baseline, 6 and 12 mo, and then annually	• Additional assessments may be added based on 12-mo results
Muscle strength	Baseline, 6 and 12 mo, and then annually	• Dynamometer if available; grip and pinch strength
Pain	Baseline, 6 and 12 mo, and then annually	• Tools such as CHAQ (73) and PODCI (74) may be considered • Recommended more frequently beyond 12 mo if initial assessment identifies need for follow-up (i.e., patients with minimal pain do not require further testing)
QOL	Baseline, 6 mo, and then annually	• HPP-specific scale is desired
GI	Baseline, 6 and 12 mo, and then annually	• Monitoring for gastroesophageal reflux and aspiration (recurrent choking, pneumonia)
Nutrition	Baseline and then annually	• Nutritional assessment, including calcium intake in diet, vitamin use, and vitamin D_3
Safety	See **Table 8**	

6MWT, 6-Minute Walk Test; BMD, bone mineral density; CHAQ, Childhood Health Assessment Questionnaire; DXA, dual energy X-ray absorptiometry; ENT, ear, nose, and throat specialist; GI, gastrointestinal; HPP, hypophosphatasia; OT, occupational therapist; PODCI, Pediatric Outcomes Data Collection Instrument; PT, physical therapist; QOL, quality of life; RSS, Rickets Severity Scale.

Mobility may be difficult to assess in young children. The Alberta Infant Motor Scale (63) and Gross Motor Function Measure (64) are recommended for younger children. For ambulatory children aged ≥5 years, baseline and follow-up assessments of mobility using the 6-Minute Walk Test (6MWT) (72), performed by an experienced physical therapist in accordance with American Thoracic Society guidelines (75), are recommended. When possible, the 6MWT may be recorded on video to allow comparison of gait and mobility over time. Based on the patient's age, the Bayley Scales of Infant and Toddler Development, Third Edition (age ≤42 months) (62) and the Peabody Developmental Motor Scales (birth through age 5 years) (71), are helpful for monitoring motor milestones in children. .

Pain and QOL are important to assess periodically throughout a patient's treatment. Changes in analgesic medication and dosage can be monitored to identify possible changes in pain levels. Pain may be assessed using the Childhood Health Assessment Questionnaire (73) and the Pediatric Outcomes Data Collection Instrument (74). QOL assessments become more important and more straightforward in older compared with younger children. The PedsQL (76) may be helpful for monitoring QOL; however, there is still a need for an HPP-specific QOL scale.

Adults

Monitoring recommendations for adults are summarized in **Table 6**. Depending on clinical presentation, prevailing symptoms, and national/regional medical practice, a full skeletal survey of adults can be completed at baseline. Bone biopsy can be considered,

particularly for patients with additional skeletal risk factors beyond HPP, such as chronic kidney disease, history of fractures, or very low BMD. Re-evaluation during treatment can help determine if bone quality and structure are improved by enzyme replacement therapy. Although BMD variations during treatment have not been systematically assessed in HPP patients, DXA may be considered before treatment to assess fracture risk and detect changes during treatment. However, DXA results should be interpreted with caution, as HPP bone characteristics might affect findings and underlying metabolic changes do not allow fracture risk to be derived from T-Scores analogous to osteoporosis testing. Osteomalacia in HPP can also confound interpretation of DXA results with normal or slightly osteopenic results. Further, normal DXA results do not necessarily rule out bone disease or risk of fracture. Although interpretation of DXA findings in HPP and associated changes during enzyme replacement therapy are not yet established, such data are likely to become available in the future to guide recommendations, for example, in terms of dosing of supportive/additional treatment modalities. To screen for changes in scoliosis or development of compression fractures, height measurements on a calibrated stadiometer are recommended at every visit.

Table 6. Monitoring recommendations for adult patients with HPP treated with asfotase alfa

Assessment	Frequency	Special Considerations
Radiograph	Baseline and 1 y; as clinically indicated	• Comprehensive skeletal survey at baseline as appropriate • Should be read by a radiologist experienced in recognizing skeletal dysplasias • Detection of pseudo-fractures and insufficiency fractures*
DXA	At physician's discretion; at least every 5 y	• Initial evaluation of fracture risk beyond HPP • Absolute BMD values to monitor changes over time
MRI	As clinically indicated	• Early detection of stress and insufficiency fractures and bone marrow edema • Joint monitoring
Bone biopsy	Baseline and follow-up during treatment if indicated by bone turnover markers, at the discretion of the clinician	• Particularly in patients with additional skeletal risk factors • Risk of fracture possible at site of biopsy • Needs to collected, processed, and read by team experienced in metabolic bone disorders
Dental	Baseline and then routine dental visits	• Provide a note to dentist to alert if changes are observed (i.e., premature tooth loss, abnormal dentition, dental caries, enlarged pulp changers of teeth (77)) or treatment with asfotase alfa is initiated
Mobility	Baseline, 3, 6, and 12 mo, and then annually	• Not in conjunction with bone biopsy (as pain from biopsy may impact ambulation) • 6MWT (72)

Assessment	Frequency	Special Considerations
Muscle strength	Baseline, 3, 6, and 12 mo, and then annually	• Dynamometry
Gait	Baseline, 3, 6, and 12 mo, and then annually	• Videotape gait or use GAITRite™, if available; otherwise, perform observational gait analysis
Pain	Baseline, 3, 6, and 12 mo, and then annually	• Wong-Baker FACES Pain Rating Scale (78); 0–10 numeric pain rating scale (79) • Collect use of medications for pain relief, loss of work
QOL	Baseline, 6 mo and 12 mo, and then annually	• Recommend EQ-5D-5L: well validated, multiple languages, 2 pages/5 questions. • Recommend a scale to follow (e.g., SF-36 (80))
GI	As clinically indicated	• Emerging natural history data indicates that functional GI disorders or feeding issues may be present in patients with HPP • GI consult may be needed
Nutrition	Baseline and as clinically indicated	• Not necessary for all
Safety	See **Table 8**	

*An insufficiency fracture is caused by normal stress on a weakened bone (81). Pseudo-fractures are a type of insufficiency fracture, which on radiograph, appear as narrow radiolucent bands composed of poorly mineralized excess osteoid across the cortex (82).

6MWT, 6-Minute Walk Test; BMD, bone mineral density; DXA, dual energy x-ray absorptiometry; EQ-5D-5L, EuroQol 5-dimension 5-level health questionnaire; GI, gastrointestinal; HPP, hypophosphatasia; MRI, magnetic resonance imaging; QOL, quality of life; SF-36, Medical Outcomes Study Short Form-36 Health Survey.

Assessments of mobility and musculoskeletal function such as the 6MWT (72), Chair Stand Test (83), and Short Physical Performance Battery (84) are recommended. Mobility assessments can be videotaped to allow comparisons over time, although subtle changes may be difficult to interpret. Evaluation of muscle strength and power is useful to monitor effects during treatment. Muscle performance can be assessed using function assessments (e.g., Bruininks-Oseretsky Test of Motor Proficiency, Second Edition [BOT-2]) and handheld dynamometry. However, it should be noted that the BOT-2 is validated only for patients aged 4–21 years (85). In adult patients, changes in medication and dosage of analgesics can be monitored to identify possible changes in pain levels. QOL may be assessed using a questionnaire such as the Medical Outcomes Study Short Form-36 health survey (80).

MANAGEMENT OF PERCEIVED TREATMENT FAILURE

The panel recommended additional assessments for identifying a lack of improvement or treatment failure in patients receiving asfotase alfa. For infants who do not exhibit skeletal improvement after 3 to 6 months of treatment (or in children after 6–9 months) or children who stop having improvement in mineralization and/or show recurrence of symptoms, additional radiographs and laboratory tests, including ALP, PLP, PTH, calcium, vitamin D, PO_4, magnesium, urine calcium/creatinine ratio can be performed. Immunoglobulin G (IgG) anti–asfotase alfa antibody testing is not currently commercially available; it is available for research use only and through the HPP registry (www.hppregistry.com). Weight and length/height in infants and children should increase steadily and progress along percentile lines during treatment with asfotase

alfa. If growth is not observed, inadequate nutrition or development of musculoskeletal conditions, such as scoliosis, should be considered. Similarly, the lack of an increase in head circumference should prompt further investigation of possible craniosynostosis. It is also important to assess the role of antibodies and compliance in a patient with perceived treatment failure. Based on the findings and discussion with the patient, parent, or caregiver, the physician can consider adjusting the dose according to the prescribing information.

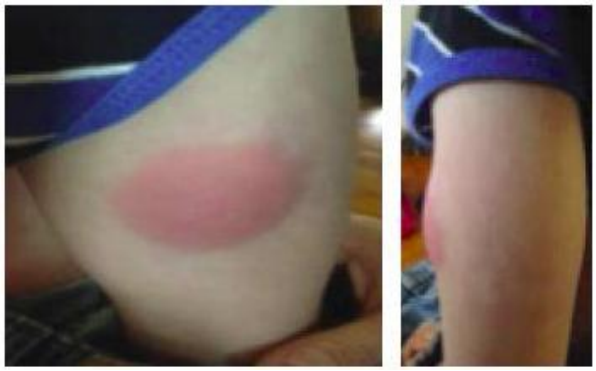
SAFETY MONITORING

Injection site reactions (ISRs)

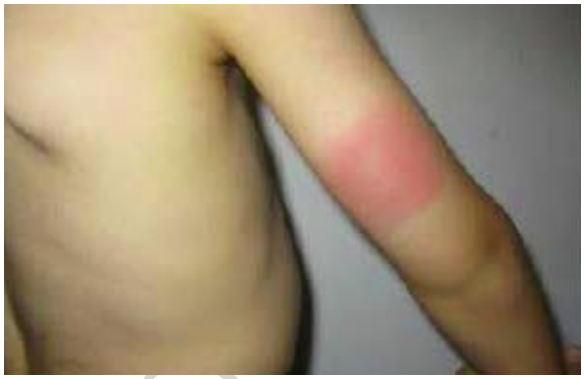
The most common adverse events (AEs) in patients treated with asfotase alfa are ISRs, occurring in approximately 73% of patients in clinical studies (40). ISRs include injection site erythema, discoloration, pain, pruritus, swelling, induration, macule, bruising, and nodules, among others (37). **Figure 2** shows images of typical ISRs after subcutaneous injections of asfotase alfa.

Figure 2.

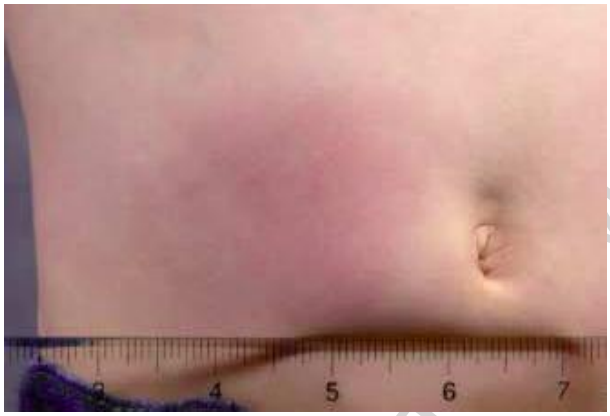
A.



B.



C.



D.

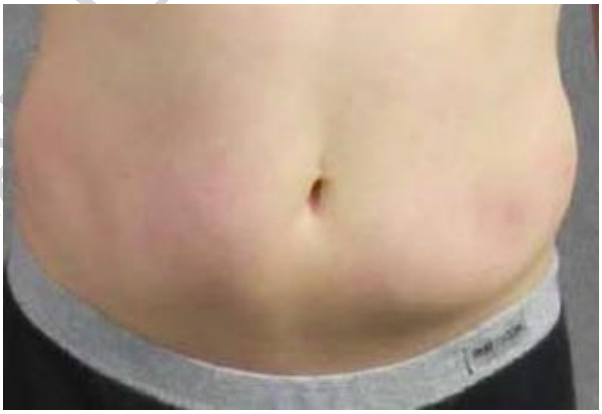


Figure 2. Images of typical injection site reactions observed after subcutaneous administration of asfotase alfa: (**A**) transient erythema with warmth and nodules; (**B**) erythematous reaction occurring in the first months of injections that later disappeared (note that erythematous reactions can occur quickly, even after the first injection); (**C**) purple discoloration at the injection site that typically appears later and is persistent; (**D**) abdominal lipohypertrophy after 4 years of treatment.

Clinicians should ensure patients, parents, and caregivers are educated regarding proper injection technique before allowing independent administration by caregivers. Asfotase alfa is dosed based on weight and is available in multiple different strength vials. Clinicians should refer to the prescribing information for appropriate guidance on vial configuration for the weight and dose for the patient (37, 40, 86-88). The 80 mg/0.8 mL vial of asfotase alfa is not recommended in the United States for pediatric patients weighing <40 kg because the systemic exposure of asfotase alfa achieved is lower than that achieved with the other strength vials (37). Basic guidance on proper injection technique is also available in the prescribing information (37, 40, 86-88). **Table 7** summarizes recommendations for administration of asfotase alfa based on guidance in the prescribing information (37, 40) and the combined opinion of the panel of physicians and nurses. Vials of asfotase alfa must be refrigerated (2–8 °C), but equilibrating the vial to room temperature by removing from refrigeration ≥15 minutes before injection may reduce risk of ISRs. The drug must be administered within 1 hour after removal from refrigeration (37). A larger bore needle (e.g., 21–27 gauge) is recommended for drawing up the dose but should be changed to a smaller bore needle for administration (e.g., 29–31 gauge), with a length sufficient to penetrate the dermal space. Injection sites should be rotated among the abdominal area, thigh, and deltoid areas to reduce risk of lipohypertrophy and injection site atrophy (use of a rotation scheme can help ensure consistent rotation). Areas that are hot, reddened, inflamed, thickened, hardened, or swollen should not be injected until these resolve. Antihistamines or acetaminophen may be taken to manage ISRs. There may be fewer ISRs with administration 3 rather than 6 times per week, although less frequent administration will

require injection of a larger volume. For dose volumes >1 mL, the injection volume should be split equally between 2 syringes and 2 injection sites (37).

Table 7. Recommendations for administration of asfotase alfa (37, 40)

Technique	Recommendation
Preinjection preparation	• Allow asfotase alfa to reach room temperature before injecting (remove from refrigeration at least 15 min before injection) (37) • Inject within 1 hour of removal from refrigeration (37, 40) • Use good sterile technique (wipe site with alcohol wipe before injecting; always use a new syringe and needle) (37) • Skin prep: ethylene glycol or lidocaine spray may reduce stinging • Pinch skin before injection
Syringe use/injection	• Use a large-gauge needle (e.g., 21–27 gauge) to pull medication from the vial • Change to a small-gauge needle (e.g., 29–31 gauge) to administer
Injection technique	• Always inject into the subcutaneous tissue and not the skin • Inject at 45- or 90-degree angle (45-degree angle for patients with little fat) • Asfotase alfa can be injected into 3 places in the body: abdominal area, thigh, or deltoid (37) – Abdomen: always inject ≥2 inches away from the umbilical cord – Thighs: use the front or outer aspects of both thighs ≥4 inches above the knees AND 4 inches below the uppermost part of the thighs; avoid the inner aspect of the thighs at all costs – Upper or outer aspects of both upper arms: may be more difficult to inject here as there may not be enough subcutaneous tissue to enable a good pinch
Frequency of injection	• Administering asfotase alfa 2 mg/kg 3 times per wk may help reduce the frequency of ISRs compared with administration 6 times per wk • Split larger volume (>1 mL) into 2 syringes for 2 injections at separate sites (37, 40)

Site rotation	• Do not administer injections in areas that are hot, reddened, inflamed, thickened, hardened, or swollen (37) • Rotate injection sites (37, 40); use a rotation scheme to ensure consistency in rotation • Always keep a log to ensure that you are keeping track of your rotation schedule • Inject into different spots even in the same quadrant to avoid injecting into the exact same spot (using a stencil might help)

ISRs, injection site reactions.

Initial follow-up should be conducted within 2 weeks of treatment initiation to obtain information on AEs including ISRs, medication storage, and patient concerns about the injection. In addition, patients can be asked to keep a log of any AEs including ISRs, and clinicians should ask questions about AEs at every clinic visit to better understand patient concerns. This will also allow for education of patients, parents, and caregivers on appropriate injection technique and the importance of continuous routine monitoring.

ISRs should be treated empirically, depending on the severity of the reaction. Some recommendations for management of ISRs are included in **Table 8**; these recommendations may change as nurses and physicians gain experience with the administration of asfotase alfa in the clinical setting.

Table 8. Recommendations for monitoring and management of adverse events in patients with HPP treated with asfotase alfa

Adverse Event	Description	Monitoring/Management Recommendations
Hypersensitivity reactions	• Signs and symptoms consistent with anaphylaxis, including difficulty breathing, choking sensation, nausea, periorbital edema, and dizziness have occurred within minutes after subcutaneous administration of asfotase alfa and can occur in patients on treatment for >1 y • Other hypersensitivity reactions have been reported, including vomiting, fever, headache, flushing, irritability, chills, skin erythema, rash, pruritus, and oral hypoesthesia	• Educate/discuss at every visit • Avoid injection if fever or anesthesia on same day • Do not schedule vaccinations on same day as injection (may require missing dose if patient is receiving asfotase alfa daily) • If a severe hypersensitivity reaction occurs, discontinue asfotase alfa and consider initiating appropriate medical treatment including: – Administer epinephrine – Administer antihistamine – Administer IV corticosteroids – Manage fluid volume/hypotension with IV fluids – For respiratory symptoms, administer a β-agonist (e.g., albuterol) via metered-dose inhaler or nebulizer – For significant dyspnea, cyanosis, or wheezing, administer moderate- to high-flow oxygen by nasal cannula or mask – Initiate advanced CPR, if necessary • Consider the risks and benefits of readministering asfotase alfa after a severe reaction; if decision is made to

Adverse Event	Description	Monitoring/Management Recommendations
		readminister, monitor patients for a reoccurrence of signs and symptoms of a severe hypersensitivity reaction and ensure access to epinephrine or other appropriate prescribed medication
ISRs	• Local ISRs including erythema, rash, discoloration, pruritus, pain, papule, nodule, and atrophy • These have been generally assessed as nonserious, mild to moderate in severity, and self-limiting	• Monitor at each clinical assessment • Advise patients to follow proper injection technique and to rotate injection sites • Ask patients to keep a diary to record ISRs • For mild to moderate events or recurrent mild events the following is recommended (can be administered 1 hour before injection): – Antihistamine (diphenhydramine, hydroxyzine, or chlorpheniramine) plus acetaminophen or ibuprofen • Include dermatologist evaluation if indicated • Administration of asfotase alfa should be interrupted in any patient experiencing severe injection reactions, and appropriate medical therapy should be administered (40)
Lipodystrophy	• Localized lipodystrophy, including lipoatrophy and lipohypertrophy, has been reported at injection sites after several months in patients treated with asfotase alfa in clinical studies	• Monitor at each clinical assessment • Advise patients to follow proper injection technique and to rotate injection sites
Hypercalcemia	• Although calcium restriction is often recommended in patients with HPP to manage	• Monitor serum PTH, calcium, phosphorous, and 25(OH)D concentrations as needed in acute hypercalcemia until

Adverse Event	Description	Monitoring/Management Recommendations
and hypocalcemia	hypercalcemia, once asfotase alfa has been initiated, restrictions may be reversed and supplementation may be required to maintain PTH within normal range (13, 38, 40)	controlled • Calcium levels should be monitored very closely after initiating asfotase alfa in perinatal/infantile patients • Calcium and vitamin D supplementation may be needed during treatment
Craniosynostosis	• Can lead to increased intracranial pressure • In clinical studies of asfotase alfa, craniosynostosis (including worsening of pre-existing craniosynostosis) was reported in HPP patients age <5 y • There are insufficient data to establish a causal relationship between exposure to asfotase alfa and progression of craniosynostosis	• Monitor at baseline, every 3 mo for the first year, and then every 6 mo for patients age <3 y and annually for patients age >3 y, depending on clinical need • Monitor for cranial deformation; premature closing fontanel; bulging; edema, calcification; head circumference • Ophthalmic examination (fundoscopy for signs of papilledema) • Neurologic examination • Cranial CT as clinically indicated if craniosynostosis is suspected • Prompt intervention for increased intracranial pressure in patients age <5 y (40)
Ectopic eye calcification	• Ophthalmic (conjunctival and corneal) calcification has been reported in patients with HPP in clinical studies of asfotase alfa (40) • There are insufficient data to establish a causal relationship between exposure to	• Ophthalmic examination at baseline and every 1 y or as clinically indicated

Adverse Event	Description	Monitoring/Management Recommendations
	asfotase alfa and ectopic eye calcifications	
Nephrocalcinosis	• Nephrocalcinosis has been reported in patients with HPP in clinical studies of asfotase alfa (89) • There are insufficient data to establish a causal relationship between exposure to asfotase alfa and nephrocalcinosis	• Renal ultrasound and urinary Ca/Cr at baseline and every 6 mo, as clinically indicated • Monitor during acute phase until stable • Assess at baseline and every 3 mo in perinatal/infantile patients and at baseline, 6 mo, and then annually in children and adults

Ca/Cr, calcium/creatinine ratio; CPR, cardiopulmonary resuscitation; CT, computed tomography; HPP, hypophosphatasia; ISR, injection site reaction; OHD, 25-hydroxyvitamin D; IV, intravenous; PTH, parathyroid hormone.

Hypersensitivity reactions

Hypersensitivity reactions, including signs and symptoms consistent with anaphylaxis, have been reported in patients receiving asfotase alfa. These include difficulty breathing, nausea, periorbital edema, dizziness, vomiting, fever, headache, flushing, irritability, chills, skin erythema, rash, pruritus, and oral hypoesthesia. Reactions have occurred within minutes after subcutaneous administration of asfotase alfa and can occur for the first time in patients who have received treatment for more than 1 year (37). If these reactions occur, immediate discontinuation of asfotase alfa is recommended and appropriate medical treatment should be initiated after current medical standards for emergency treatment. Clinicians need to maintain an index of suspicion for hypersensitivity or anaphylactic reactions. Rechallenge of patients who have experienced hypersensitivity reactions should be in a clinical setting where they can be adequately observed. Not all patients may need to be prescribed self-injectable epinephrine; however, the panel recommended a prescription for those who have previously experienced any systemic hypersensitivity reaction beyond an ISR or based on the physician's judgment. Additionally, based on experience with other enzyme replacement therapies, panel members recommend that administration of asfotase alfa not be scheduled on the same day as a vaccination or if the patient has a fever of >103°F. Measurement of immunoglobulin E, tryptase, and complement levels may also be useful after hypersensitivity reactions.

Additional safety assessments

AEs observed in clinical studies of asfotase alfa were usually of mild to moderate intensity, were usually not attributed to the drug, and were consistent with

manifestations of HPP (37, 90). Regardless of asfotase alfa treatment, patients with HPP are at increased risk for developing ectopic calcifications (37). Calcifications of the eye (cornea and conjunctiva) and kidneys were reported in clinical trials of asfotase alfa; no visual changes or changes in renal function associated with the calcifications were reported. Cases of ectopic calcification after initiation of treatment with asfotase alfa were noted to be self-limiting. In some cases, evidence was insufficient to determine whether events were consistent with the disease or a result of treatment (37). Craniosynostosis (associated with increased intracranial pressure), including worsening of pre-existing craniosynostosis, was reported in 4 of 10 patients in a clinical study of asfotase alfa in HPP patients aged <3 years (38), although whether this is associated with underlying disease progression has not been elucidated.

Panel recommendations for monitoring and management of AEs are summarized in **Table 8**. Consistent with prescribing information (37, 40), advisory panel members recommend ophthalmologic examinations and renal ultrasounds be performed at baseline and periodically during treatment to monitor for signs and symptoms of ectopic calcifications and changes in vision and renal function. Periodic monitoring for craniosynostosis, including fundoscopy for signs of papilledema, and prompt intervention for increased intracranial pressure are recommended for patients younger than age 5 years. For perinatal and infantile patients, the panel recommends that an ophthalmologist follow-up every 3 months for the first year and every 6 months thereafter to monitor for increased intracranial pressure and ectopic eye calcifications in addition to clinical monitoring. The panel also advises that adult

patients at increased cardiovascular risk be monitored for vascular calcifications per standard guidelines (91).

Calcium restriction is often recommended in infants/children with HPP to manage hypercalcemia. Once treatment with asfotase alfa has been initiated, restrictions may be lifted and supplementation with additional calcium may be required to maintain PTH within the normal range (13, 38, 40) (**Table 8**). As such, serum calcium, phosphorous, vitamin D, and PTH levels should be monitored very closely after initiating asfotase alfa in these patients (as described in **Table 3**). In perinatal and infantile patients, ionized calcium should be measured; if ionized calcium testing is not available, albumin levels are needed to interpret calcium findings.

Across 5 clinical studies, efficacy was not reduced even though antidrug antibodies were detected (40). Anti–asfotase alfa antibody measurement may be considered a goal for patients currently on commercial treatment; however, it is not currently available commercially in the clinical setting. Anti–asfotase alfa antibody measurement is available for research use only and through the HPP Registry. Interpretation of results and impact on patient management remains to be determined.

DISCUSSION

HPP is a systemic, metabolic disease with onset of signs and symptoms ranging from in utero to adulthood and a variety of clinical features and complications (1, 2, 13, 26). Enzyme replacement therapy with asfotase alfa is an approved treatment for patients with HPP (37, 90). The primary goal of treatment, to treat bone

manifestations of the disease, extends to goals related to the sequelae of bone manifestations, which range from improved growth and mobility to improved ventilatory status, to survival, among others (**Table 2**). The current consensus recommendations provide a basic framework for monitoring patients with HPP for whom the decision to treat has been made. However, the treatment and monitoring of patients with HPP should be tailored to the patient based on the individual's medical history and clinical manifestations and may vary from country to country.

Several unmet needs remain in the assessment of patients with HPP who are receiving asfotase alfa. For example, standardized, commercially available assays for PPi, direct measurement of PLP, and immunogenicity on treatment will have clinical utility in the overall management of HPP. In addition, a HPP-specific tool is needed to assess QOL. Given accumulating data on asfotase alfa and HPP, guidance offered in this consensus report will continue to evolve.

An HPP registry (www.hppregistry.com) has been established to better understand both the natural history of HPP and to monitor and evaluate long-term treatment effects of asfotase alfa. Patients and their caregivers should be encouraged to contribute their data to the registry.

CONCLUSIONS

Because of the systemic manifestations of HPP, a coordinated, multidisciplinary, team-based and patient-focused approach is needed for managing patients receiving asfotase alfa therapy. These consensus recommendations are based on the expert opinion of physicians experienced in the management of HPP and are intended to

serve as a basic framework for monitoring patients with HPP for whom the decision to treat has been made. However, monitoring assessments must be tailored to the individual patient, depending on medical history, specific clinical manifestations, and the clinician's professional judgment. Clinicians are reminded that the recommendations provided may evolve as more scientific information becomes available.

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