Pediatric and Perinatal Patient With Hypophosphatasia (HPP) Clinical Criteria Checklist

Patient Name:

DOB: **Sex:** Select Sex **MRN:**

Primary Phone: (**)** **–** **Date:**

GUIDANCE FOR HEALTHCARE PROVIDERS (HCPs)

This HPP clinical criteria checklist is an educational resource to assist HCPs in triaging patients suspected of having HPP who are under 18 years of age including the perinatal period (*in utero* or at birth) for further evaluation and diagnosis. This checklist is not intended to serve as clinical guidelines. It is the sole responsibility of the HCP to make a diagnosis based on in-person patient evaluation. Please refer to the *Adult with Hypophosphatasia (HPP) Clinical Criteria Checklist* for a more complete workup of an adult patient.

DISEASE SUMMARY

HPP is a rare, inherited, progressive metabolic disease caused by deficient alkaline phosphatase (ALP) enzyme activity. Due to the multisystemic heterogeneity of HPP symptoms, diagnoses are often delayed or missed.[1,2]

NEED FOR EARLY DIAGNOSIS

Severe HPP occurs in 1 in 300,000 births and milder HPP has been reported in some sources to occur in up to 1:6,370 births.[3] The overall incidence and prevalence of all forms of HPP are not known. Complications can occur at any age and can lead to significant disability.[4,5] There are often delays in diagnosis even after fractures or dental problems due to lack of clinician awareness.[6] Early diagnosis is essential for appropriate patient management.[6]

DIAGNOSTIC CRITERIA

The criteria used to help inform an HPP diagnosis include persistently low age- and sex-adjusted ALP levels, clinical signs and symptoms of HPP, and ruling out other causes of low ALP levels as demonstrated in **Figure 1**. If all three criteria are met, then there is sufficient evidence to support an HPP diagnosis as shown in **Figure 2**.

Figure 1[2,7,8]

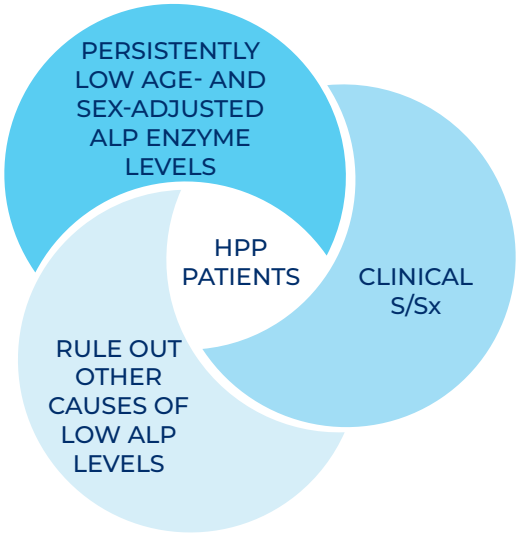
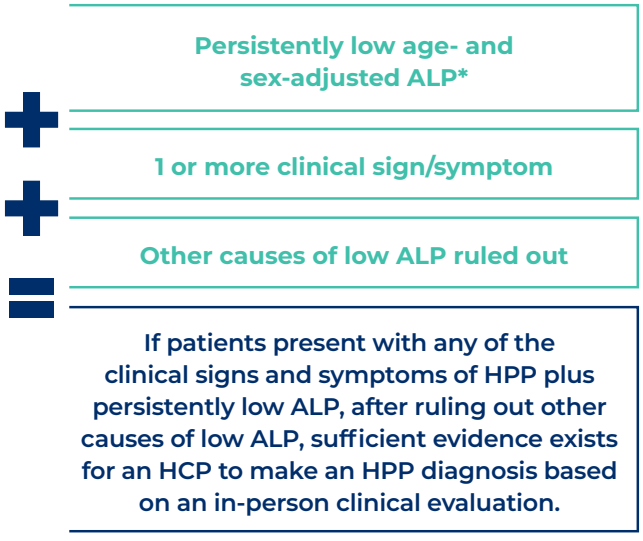


Figure 2[2,5,9]



*Refer to your lab for appropriate age- and sex-adjusted reference range or see **Table 1** for illustrative examples of reference ranges on some diagnostic platforms.

Keep track of the diagnostic criteria in the tables on the following pages. Check yes or no and add additional notes (if needed) in each box to keep track of assessed criteria.

ALP levels[5,7,8,10]

Please note: Pediatric patients exhibit higher baseline ALP levels due to differences in osteoblast activity and other factors related to development.[11,12] Children may have deficient ALP activity that goes undetected if reference intervals are not appropriately adjusted by age and sex.[13,14]

	Yes	No	Additional notes (eg, lab values, serum, or plasma)	
Does the patient have persistently low age- and sex-adjusted ALP levels (may be defined as at least 2 values below normal within 6 months)? • Laboratory ALP reference ranges should be adjusted for age and sex (see **Table 1** below)[a]	☐	☐		
			Dates	**ALP level (U/L)**

a. ALP reference levels may vary from population to population in addition to age and sex. Local institutions' diagnostic laboratories should develop local reference intervals.[13,15] Variations exist between testing platforms, and each platform should have a specific, validated reference range.[13]

Table 1. Validated lower limit of normal ALP by age and sex across platforms[13,16,17]

The Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) is a laboratory initiative developing comprehensive pediatric reference intervals for a number of biomarkers, eg, ALP. CALIPER meets the standards set by the Clinical and Laboratory Standards Institute based on C28-A3 and EP9-A2 guidelines and is developing validated reference intervals for dozens of diseases across 6 major diagnostic platforms and can provide a framework for developing local pediatric reference intervals. Adopting accurate reference intervals, such as CALIPER, can improve accurate and timely diagnosis, particularly among pediatric patients.

	Abbott ARCHITECT		Beckman Coulter DxC		Beckman Coulter AU		Ortho VITROS		Roche Cobas		Siemens Vista[a]	
Age range LLN*	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
0-<15 days	90	90	77	77	76	76	91	91	83	83	81.5	81.5
15 days-<1 year	134	134	116	116	113	113	131	131	122	122	121.7	121.7
1-<10 years	156	156	135	135	132	132	151	151	142	142	141.8	141.8
10-<13 years	141	141	122	122	119	119	137	137	129	129	128.1	128.1
13-<15 years	62	127	52	109	52	107	66	124	57	116	55.5	114.9
15-<17 years	54	89	46	77	45	75	59	91	50	82	48.7	80.9
17-<19 years	48	59	41	50	40	49	54	64	45	55	43.1	53.2

LLN, lower limit of normal.

*These are the LLN values for ALP levels in each age range.

ALP levels are shown in U/L. Values in **orange** are lower limits of normal that differ between male and female. Refer to your lab for appropriate age- and sex-adjusted reference range.

Pediatric Clinical Signs and Symptoms (may also appear in adult patient medical histories)

Please note: Pediatric signs and symptoms may overlap with adult signs and symptoms. Pediatric signs and symptoms may also appear in adult medical histories. (Please refer to the *Adult with Hypophosphatasia (HPP) Clinical Criteria Checklist* as well for a more complete workup of an adult patient with HPP.)

	Were any of the following observed in patient and document earliest age of sign/symptom onset:	Yes	No	Additional notes (eg, ICD-10-CM code, SNOMED, lab values)	Dates (eg, date of symptom onset)
PERINATAL HPP (*in utero* or at birth) Signs and Symptoms (Not an exhaustive list)[5,18,19]:					
 **SKELETAL**	Hypoechogenic/hypomineralized skull?	☐	☐		
	Short, beaded, or thin ribs?	☐	☐		
	Inconsistent ossification of vertebrae?	☐	☐		
	Reduced mineralization of hands?	☐	☐		
	Deficient or absent ossification of bones?	☐	☐		
	Metaphyseal radiolucencies?	☐	☐		
	Fractures/low trauma fractures?	☐	☐		
	Osteochondral spurs (Bowdler spurs)?	☐	☐		
	Ectopic calcification (eg, nephrocalcinosis and ophthalmic calcification)?	☐	☐		
 **DEVELOPMENT/ GROWTH**	Skeletal deformities (eg, shortened or bowed limbs or enlarged wrists, knees, and ankles)?	☐	☐		
	Shortening, bowing, angulation of long bones?	☐	☐		
	Clubfoot?	☐	☐		
	Stillbirth?	☐	☐		
	Severe chest deformity?	☐	☐		
 **NEUROLOGICAL**	Seizures?	☐	☐		
 **RESPIRATORY**	Apnea?	☐	☐		
INFANTILE HPP (birth to <6 months) Signs and Symptoms (Not an exhaustive list)[5,18,19]:					
 **SKELETAL**	Rickets?	☐	☐		
	Fractures/low trauma fractures?	☐	☐		
	Craniosynostosis?	☐	☐		
	Ectopic calcification (eg, nephrocalcinosis and ophthalmic calcification)?	☐	☐		

	Were any of the following observed in patient and document earliest age of sign/symptom onset:	Yes	No	Additional notes (eg, ICD-10-CM code, SNOMED, lab values)	Dates (eg, date of symptom onset)
INFANTILE HPP (birth to <6 months) Signs and Symptoms (Not an exhaustive list) (cont.)[5,18,19]:					
DEVELOPMENT/ GROWTH	Skeletal deformities (eg, shortened or bowed limbs or enlarged wrists, knees, and ankles)?	☐	☐		
	Poor feeding?	☐	☐		
	Poor weight gain?	☐	☐		
	Failure to thrive?	☐	☐		
NEURO-LOGICAL	Vitamin B6 responsive seizures?	☐	☐		
RESPIRA-TORY	Respiratory insufficiency?	☐	☐		
	Respiratory failure?	☐	☐		
RENAL	Hypercalcemia/hypercalciuria?	☐	☐		
MUSCULAR	Hypotonia?	☐	☐		
CHILDHOOD HPP (≥6 months to <18 years) Signs and Symptoms (Not an exhaustive list)[5,18,19]:					
SKELETAL	Rickets?	☐	☐		
	Low trauma fractures/poorly healing or recurrent fractures?	☐	☐		
	Craniosynostosis?	☐	☐		
	Ectopic calcification?	☐	☐		
	Bone and/or joint pain?	☐	☐		
DEVELOPMENT/ GROWTH	Skeletal deformities (eg, shortened or bowed limbs or enlarged wrists, knees, or ankles)?	☐	☐		
	Delayed walking?	☐	☐		
	Delayed/missed motor milestones?	☐	☐		
	Short stature?	☐	☐		
DENTAL	Premature loss of primary teeth?	☐	☐		
MUSCULAR	Muscle pain?	☐	☐		
	Waddling gait?	☐	☐		
	Muscle weakness?	☐	☐		

Other potential causes of low ALP levels (Not an exhaustive list)[2,8,b]

Can you rule out...	Yes	No	Additional notes (eg, ICD-10-CM code, SNOMED, lab values)	Dates (eg, date of symptom onset)
Cleidocranial dysplasia/dysostosis?	☐	☐		
Mseleni joint disease?	☐	☐		
Benign familial hypophosphatasemia?	☐	☐		
Osteogenesis imperfecta type II?	☐	☐		
Profound hypothyroidism?	☐	☐		
Cushing's disease?	☐	☐		
Bisphosphonate therapy?	☐	☐		
Adynamic renal osteodystrophy?	☐	☐		
Milk-alkali syndrome?	☐	☐		
Vitamin D intoxication?	☐	☐		
Wilson disease?	☐	☐		
Nutritional deficiencies (vitamin C)?	☐	☐		
Hypomagnesemia?	☐	☐		
Hypozincemia?	☐	☐		
Celiac disease?	☐	☐		
Pernicious anemia?	☐	☐		
Radioactive heavy metal contamination?	☐	☐		
Cardiac bypass surgery?	☐	☐		
Major trauma?	☐	☐		
Surgery?	☐	☐		
Cancers and chemotherapy?	☐	☐		
Multiple myeloma?	☐	☐		
Blood transfusion?	☐	☐		
Starvation/acute caloric restriction?	☐	☐		
Sepsis/multi-organ/hepatic failure?	☐	☐		
Analytic error?	☐	☐		
Improperly collected specimen?	☐	☐		

b. ALP levels adjusted for age and sex.

Additional tests

If patients present with any of the above clinical signs and symptoms plus persistently low ALP, after ruling out other causes of low ALP, there is sufficient evidence for an HPP diagnosis. The following laboratory tests can further support the HCP's diagnosis of HPP.

Additional test	Yes	No	Test results and additional notes	Dates
Serum pyridoxal 5'-phosphate (PLP)/vitamin B6[5] • Is the patient's PLP/vitamin B6 level elevated? • In HPP, low ALP may lead to an accumulation of PLP • PLP is the major circulating form of vitamin B6 • Levels may be high or normal[c] **c.** Special care must be taken to ensure the sample is not exposed to light during collection, as it can alter the results.[20]	☐	☐		
Urinary phosphoethanolamine (PEA) levels[5,18,21] • Is the patient's PEA level elevated? • The role of PEA has not been fully established, but in HPP urinary PEA levels may be increased • PEA levels are assessed by collecting a urine sample; however, the preferred method of collection varies (eg, spot vs 24-hour urine sample). Please consult with the specific laboratory to discuss sample type, duration and timing of collection, as urinary protein levels can vary throughout a 24-hour period	☐	☐		
***ALPL* gene testing**[5,18,22,23] • Does the patient have an *ALPL* gene mutation? • Mutations in the *ALPL* gene cause low ALP activity • A negative or inconclusive test does not exclude the diagnosis of HPP • A positive test is not required for an HPP diagnosis but may be useful for genetic counseling purposes	☐	☐		

Please contact your local Alexion Representative for questions about substrate or genetic testing for HPP.

1. Högler W, et al. Diagnostic delay is common among patients with hypophosphatasia: initial findings from a longitudinal, prospective, global registry. *BMC Musculoskelet Disord*. 2019;20(1):80. doi:10.1186/s12891-019-2420-8 **2.** Bishop N, et al. Transformative therapy in hypophosphatasia. *Arch Dis Child*. 2016;101(6):514-515. doi:10.1136/archdischild-2015-309579 **3.** Mornet E, et al. A molecular-based estimation of the prevalence of hypophosphatasia in the European population. *Ann Hum Genet*. 2011;75(3):439-445. **4.** Beck C, et al. Hypophosphatasia - recent advances in diagnosis and treatment. *Open Bone J*. 2009;1:8-15. **5.** Rockman-Greenberg C. Hypophosphatasia. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. **6.** Mori M, et al. Case series: odontohypophosphatasia or missed diagnosis of childhood/adult-onset hypophosphatasia? – Call for a long-term follow-up of premature loss of primary teeth. *Bone Rep*. 2016;5:228-232. **7.** Bianchi ML, et al. Hypophosphatasia in adolescents and adults: overview of diagnosis and treatment. *Osteoporos Int*. 2020;31(8):1445-1460. doi:10.1007/s00198-020-05345-9 **8.** McKiernan FE, et al. Acute hypophosphatasemia. *Osteoporos Int*. 2014;25(2):519-523. doi:10.1007/s00198-013-2447-x **9.** Whtye MP. Hypophosphatasia: an overview for 2017. *Bone*. 2017;102:15-25. **10.** Kim WR, et al; Public Policy Committee of the American Association for the Study of Liver Disease. Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. *Hepatology*. 2008;47(4):1363-1370. doi:10.1002/hep.22109 **11.** Lala V, et al. Liver function tests. *StatPearls*. Updated October 5, 2022. Accessed January 9, 2023. https://www.ncbi.nlm.nih.gov/books/NBK482489/ **12.** Turan S, et al. Serum alkaline phosphatase levels in healthy children and evaluation of alkaline phosphatase z-scores in different types of rickets. *J Clin Res Pediatr Endocrinol*. 2011;3(1):7-11. **13.** Etsey MP, et al. CLSI-based transference of the CALIPER database of pediatric reference intervals from Abbott to Beckman, Ortho, Roche and Siemens Clinical Chemistry Assays: direct validation using reference samples from the CALIPER cohort. *Clin Biochem*. 2013;46(13-14):1197-1219. **14.** Semler O, et al. Cross-sectional analysis: clinical presentation of children with persistently low ALP levels. *J Pediatr Endocrinol Metab*. 2021;34(12):1559-1566. **15.** Tahmasebi H, et al. Pediatric reference intervals for biochemical markers: gaps and challenges, recent national initiatives and future perspectives. *EJIFCC*. 2017;28(1):43-63. **16.** Colantonio D, et al. Closing the gaps in pediatric laboratory reference intervals: a CALIPER database of 40 biochemical markers in a healthy and multiethnic population of children. *Clin Chem*. 2012;58(5):854-868. **17.** Welcome to CALIPER. CALIPER Project. Accessed November 30, 2022. https://caliperproject.ca/ **18.** Whyte MP. Hypophosphatasia: nature's window on alkaline phosphatase function in humans. *Principles of Bone Biology*. 3rd ed. Academic Press; 2008:1573-1598. **19.** Kishnani PS, et al. Monitoring guidance for patients with hypophosphatasia treated with asfotase alfa. *Mol Genet Metab*. 2017;122(1-2):4-17. doi:10.1016/j.ymgme.2017.07.010 **20.** Light protection tests. Mayo Clinic. Updated May 10, 2021. Accessed November 30, 2022. http://www.mayocliniclabs.com/specimen/preparation/light-protection **21.** Abubacker NRT, et al. A comparative study of spot urine versus 24 hour urine in assessment of proteinuria in varying degree of renal dysfunction. *Int J Adv Med*. 2016. Accessed November 30, 2022. https://www.ijmedicine.com/index.php/ijam/article/view/218 **22.** Mornet E, et al. Hypophosphatasia. *GeneReviews®*. 2007. https://www.ncbi.nlm.nih.gov/books/NBK1150/ **23.** Khan AA, et al. Hypophosphatasia: Canadian update on diagnosis and management. *Osteoporos Int*. 2019;30(9):1713-1722.