Adult 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 suspect HPP patients 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.

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]

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[2-4]

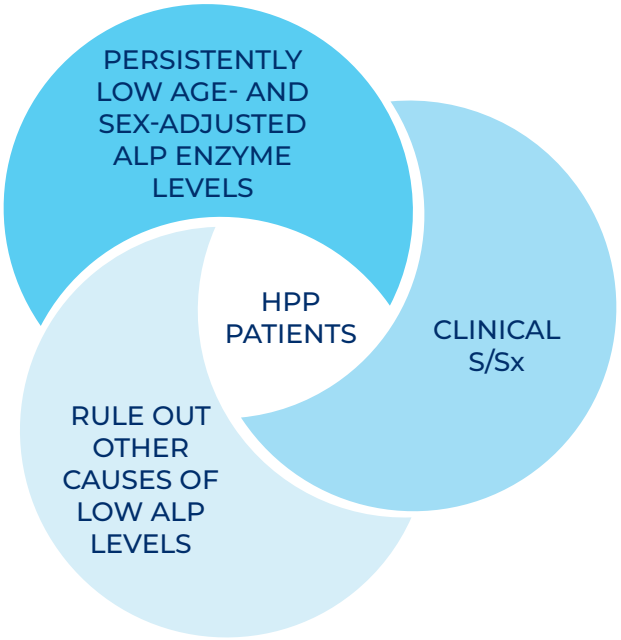

Figure 2[2,5,6]

Persistently low age- and sex-adjusted ALP (<40 U/L)*

\+

1 or more clinical sign/symptom

\+

Other causes of low ALP ruled out

=

If patients present with any of the clinical signs and symptoms of HPP plus persistently low ALP, after ruling out other causes of low ALP, sufficient evidence exists for an HCP to make an HPP diagnosis based on an in-person clinical evaluation.

*Refer to your lab for appropriate age- and sex-adjusted reference range. 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[3,4,6,7]

	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 • The lower limit of normal for ALP levels in adults is 40 U/L[8-12,a]	☐	☐		
			Dates	**ALP level (U/L)**

a. Limitations: An ALP level of below 40 U/L is not conclusive for diagnosis of HPP. Patients should be evaluated for other symptoms of HPP and differential diagnoses should be ruled out. Check with your lab for their appropriate age- and sex-adjusted reference range.

Clinical Signs & Symptoms (for adults [>18 years] with HPP) (Not an exhaustive list)

Please note: Pediatric signs and symptoms may also appear in adult patient medical histories. It is important to consider childhood symptoms while working up an adult patient. Please refer to the Childhood HPP Signs and Symptoms section for further guidance on signs and symptoms that may have been observed in the patient before the age of 18.

	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)
 SKELETAL	Fractures (low trauma fractures, delayed healing or recurrent fractures, pseudofractures, and metatarsal stress fractures)?[6,13,14]	☐	☐		
	Osteomalacia?[6,13,14]	☐	☐		
	Joint hypermobility?[15]	☐	☐		
	Bone and/or joint pain?[14,16]	☐	☐		
	Calcium pyrophosphate deposition disease (CPPD) [psuedogout]?[13,14]	☐	☐		
	History of rickets?[2,15]	☐	☐		
 DENTAL	Dental abnormalities (tooth loss, destruction of periodontal tissue)?[1,6,13]	☐	☐		
 DEVELOPMENT/ GROWTH	Skeletal deformities?[6,13,14]	☐	☐		
	Short stature?[6,13,14]	☐	☐		

Clinical Signs & Symptoms (for adults [>18 years] with HPP) (cont.)

	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)
NEUROLOGIC/ OPHTHALMOLOGIC	Fatigue?[16]	☐	☐		
	Ophthalmic calcifications?[2,13,17]	☐	☐		
RENAL	Nephrocalcinosis?[2,13,17]	☐	☐		
MUSCULAR	Muscle weakness?[14]	☐	☐		
	Muscle pain?[14,16]	☐	☐		
	Impaired mobility?[15]	☐	☐		
	Gait disturbance?[14]	☐	☐		

Childhood HPP (≥6 months to <18 years) Signs & Symptoms (Not an exhaustive list)[6,13,17]

Please note: Pediatric signs and symptoms may overlap with adult signs and symptoms. Pediatric signs and symptoms may also appear in adult medical histories. It is important to consider childhood symptoms while working up an adult patient.

	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)
SKELETAL	Rickets?	☐	☐		
	Low trauma fractures/poorly healing or recurrent fractures?	☐	☐		
	Craniosynostosis?	☐	☐		
	Ectopic calcification?	☐	☐		
	Bone and/or joint pain?	☐	☐		
DENTAL	Premature loss of primary teeth?	☐	☐		
DEVELOPMENT/ GROWTH	Skeletal deformities (eg, shortened or bowed limbs or enlarged wrists, knees, or ankles)?	☐	☐		
	Delayed walking?	☐	☐		
	Delayed/missed motor milestones?	☐	☐		
	Short stature?	☐	☐		
MUSCULAR	Waddling gait?	☐	☐		
	Muscle pain?	☐	☐		
	Muscle weakness?	☐	☐		

Other potential causes of low ALP levels (Not an exhaustive list)[2,4,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[6] • 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.[18]	☐	☐		
Urinary phosphoethanolamine (PEA) levels[6,13,19] • 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**[6,13,20,21] • 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.

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