Guidance for the investigation of low alkaline phosphatase (ALP)

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Membership of the guideline development group	**Terry Aspray, Consultant Physician (Newcastle upon Tyne Hospitals NHS FT) Marta Bertoli, Consultant in Clinical Genetics (Newcastle upon Tyne Hospitals NHS FT) Elodie Hanon, Clinical Scientist in Biochemistry (Newcastle upon Tyne Hospitals NHS FT) Gavin Mercer-Smith, Specialist Registrar in Chemical Pathology (Newcastle upon Tyne Hospitals NHS FT) Nishanti Thalayasingam, Consultant Rheumatologist (Newcastle upon Tyne Hospitals NHS FT)**
Consultees	**Nicola McNicol, Medicines Optimisation Specialist Pharmacist, NECS Helen Horton, GP and clinical lead with the ICB for North Cumbria Denis Burke, Consultant - Medicine, Gastroenterology NCIC Liz Middling, Consultant Clinical Scientist and Head of Department, Blood Sciences NCIC Ailish O'Callaghan, Elderly Care Consultant, NCIC Helen Andrews, General Practitioner , Newcastle upon Tyne**

Guidance for the investigation of low alkaline phosphatase (ALP)

1. Introduction

This guidance relates to adults with low alkaline phosphatase (ALP) with or without hypophosphatasia symptoms. This guidance does not apply to children.

Please refer to the flowchart (appendix 1) for an overview of the investigation process.

2. Why is this guidance important?

While a raised ALP is a commonly recognised marker of liver or metabolic bone disease, low levels of ALP are more rarely noted and have not been consistently reported by laboratories. There are a number of causes for a low ALP, which are presented in this guidance. A diagnosis of hypophosphatasia has important implications for adults, who may be suffering from dental problems, non-specific symptoms of chronic musculoskeletal pains, be at risk of *atypical* femur fracture and, in the event of osteoporotic fracture, must avoid usual *bone protection* therapies, such as bisphosphonates. As this is an inherited condition, genetic counselling may, occasionally, be necessary.

3. Identification of low alkaline phosphatase

The adult reference range for ALP originates from the national Pathology Harmony project, and is based on consensus involving a large number of laboratory scientists supported by professional bodies: 30 – 130 U/L.

Spurious causes of low ALP (less than 30 U/L) should be excluded. Please note contamination of serum samples with anticoagulants such as EDTA and citrate will falsely decrease ALP activity. Gross contamination will be detected by the laboratory and identified on the report.

An isolated low ALP (below the lower limit of the reference range) should be confirmed on a repeat sample, unless there is evidence of consistently low levels on previous measurement.

4. Exclude secondary causes of low alkaline phosphatase

Several conditions have been associated with low ALP activity and should be excluded: malnutrition, hypothyroidism, severe anaemia, Wilson's disease and within one-week post-cardiac surgery.

Magnesium and zinc are co-factors of ALP, so deficiencies may result in low levels. Low vitamin B12 has also been associated with low ALP activity.

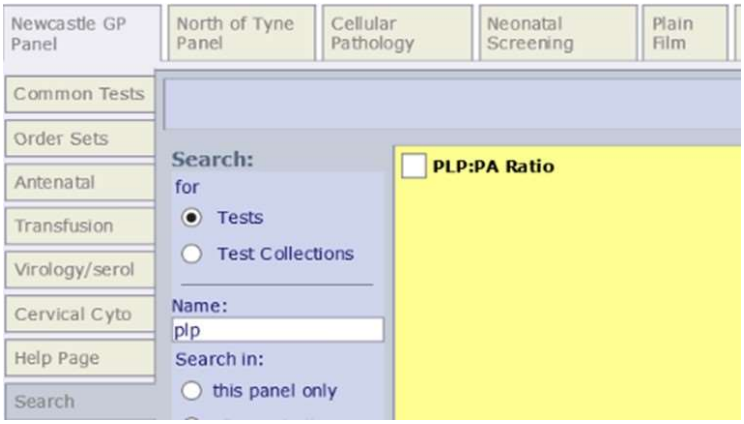
Therefore, TSH, FBC, copper, caeruloplasmin, magnesium, zinc and vitamin B12 should be measured in a patient with persistently low ALP.

Circulating concentrations of trace elements and vitamins are affected by the inflammatory (or acute phase) response. Therefore, CRP (C-reactive protein) should be requested alongside the trace elements and vitamins to aid the interpretation of results.

5. Referral to the metabolic bone service

After exclusion of secondary causes of low ALP, consideration of adult phenotype hypophosphatasia should be considered and a request made for plasma PLP:PA ratio if possible, and discuss or refer, as appropriate, with the metabolic bone service.

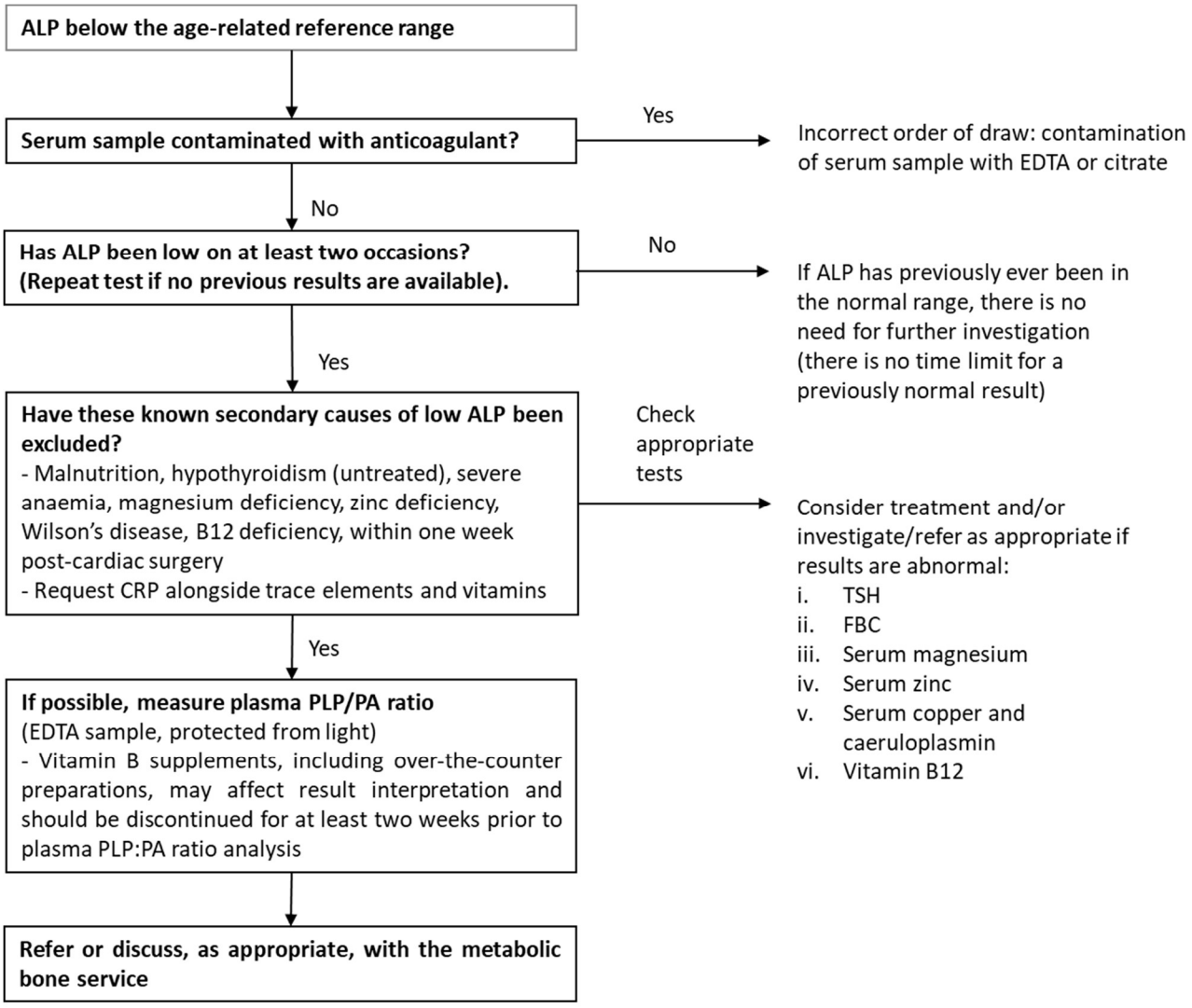
PLP:PA ratio is requestable on ICE, as shown in the screenshot below.



6. Vitamin supplementation

Vitamin B supplements, including over-the-counter preparations, may affect result interpretation. Such supplements should be discontinued for at least two weeks prior to plasma PLP:PA ratio analysis.

Appendix 1:


ALP below the age-related reference range
Serum sample contaminated with anticoagulant?
Yes
Incorrect order of draw: contamination of serum sample with EDTA or citrate
No
Has ALP been low on at least two occasions? (Repeat test if no previous results are available).
No
If ALP has previously ever been in the normal range, there is no need for further investigation (there is no time limit for a previously normal result)
Yes
Have these known secondary causes of low ALP been excluded?
- Malnutrition, hypothyroidism (untreated), severe anaemia, magnesium deficiency, zinc deficiency, Wilson's disease, B12 deficiency, within one week post-cardiac surgery
- Request CRP alongside trace elements and vitamins
Check appropriate tests
Consider treatment and/or investigate/refer as appropriate if results are abnormal:
i. TSH
ii. FBC
iii. Serum magnesium
iv. Serum zinc
v. Serum copper and caeruloplasmin
vi. Vitamin B12
Yes
If possible, measure plasma PLP/PA ratio
(EDTA sample, protected from light)
- Vitamin B supplements, including over-the-counter preparations, may affect result interpretation and should be discontinued for at least two weeks prior to plasma PLP:PA ratio analysis
Refer or discuss, as appropriate, with the metabolic bone service