LABUPDATE no. 56

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AMPATH LABORATORIES

HAEMATINIC TESTS: CHANGES TO REFERENCE RANGES AND COMMENTS

Ampath has extensively reviewed and updated some of the reference ranges and comments provided for haematinic testing to include recommendations from the most recent international and local consensus guidelines.[1,2]

1. **Changes to reference ranges for ferritin and transferrin saturation:**
   a. The *lower reference limit for ferritin* has been changed to ***30 µg/L*** and for percentage *transferrin saturation (TS)* to ***20%*** in all adults.[1,2]
   b. The ferritin unit for reporting was also updated from ng/ml to the equivalent SI unit of ug/L.
   c. These changes are mostly based on expert opinion, as previously established ranges have been found to be clinically inappropriate and were not based on well-designed studies.

2. **New recommendations on the effect of inflammation on the iron profile:**[1,2]
   a. ***Ferritin*** is a positive acute-phase protein (increases with infection or inflammation), while ***transferrin*** is a negative acute-phase protein (decreases with infection or inflammation).
   b. ***Iron deficiency (ID) can be masked by chronic inflammatory disorders***, such as obesity, insulin resistance, diabetes, chronic renal and heart failure, as well as active inflammatory bowel disease.
   c. In the presence of ***infection/inflammation, a normal ferritin below 100 µg/L is used to diagnose ID***, especially in the presence of low TS (< 20%).
   d. With ***chronic inflammatory conditions***, e.g. chronic heart failure or active inflammatory bowel disease, ID may also be present with normal ferritin above 100 µg/L, *if TS is low (<20%)*.
   e. The following ***tests may be considered to confirm ID in the presence of normal ferritin***:
      i. Soluble transferrin receptor (increased) (test mnemonic: STFR)
      ii. Reticulocyte Hb content (decreased) (test mnemonic: RET)

3. **Factors to consider when interpreting folate and vitamin B12 levels:**
   a. Always determine ***vitamin B12 levels*** in patients with ***megaloblastic anaemia***, especially if *neurological symptoms* are also present.[3]
   b. ***Folate*** should be determined additionally in patients at ***high risk of folate deficiency***, e.g. individuals with gastrointestinal conditions, excess alcohol use or who consume folate-poor diets.[3]
   c. The ***lower limit indicating vitamin B12 or folate deficiency is not well defined***. In patients with borderline-low/low-normal results, determination of ***homocysteine*** may be useful to confirm clinical significance. Methylmalonic acid (MMA) may be considered additionally to distinguish between folate and vitamin B12 deficiency:[3]
      i. *Both homocysteine and MMA elevated*: consistent with vitamin B12 deficiency (does not exclude folate deficiency)
      ii. *Homocysteine elevated with normal MMA*: consistent with folate deficiency, B12 deficiency excluded.
   d. ***Vitamin B12 levels may also be falsely normal*** in the presence of deficient liver stores of vitamin B12 if transcobalamin is elevated (e.g. due to myelo- and lymphoproliferative disorders, occult malignancy, alcoholic liver disease, kidney disease and autoimmune diseases). Homocysteine determination will also be helpful in these patients if vitamin B12 deficiency is clinically suspected.
   e. Some conditions may be associated with ***spuriously low vitamin B12 levels*** (in the absence of deficiency), including multiple myeloma, HIV infection, pregnancy, oral contraceptives and phenytoin.

f. Although ***serum folate is increased by recent intake***, this is mostly true for the intake of supplements, as a normal diet contains relatively low levels of folate.[4] If folate deficiency is suspected, but the folate level is normal, a fasting folate is recommended.
g. In general, ***serum folate*** performs *similar or slightly better compared to red cell folate* and is the ***preferred test for diagnosis of folate deficiency***, as it is the earliest abnormality detected.[4]
h. ***Serum folate is better*** compared to red cell folate for the following conditions:[4]
    i. Vitamin B12 deficiency (red cell folate may be false low in these cases due to folate trapping)
    ii. Prediction of the risk for neural-tube defects (NTD), if done during pregnancy.
    iii. Haemodialysis, if collected before dialysis.
    iv. Prediction of the risk of toxicity of capecitabine (a 5-fluorouracil prodrug).
i. ***Red cell folate*** is a better marker for long-term folate status and is the preferred marker only under the following circumstances:[4]
    i. Haemodialysis, if collected soon after dialysis.
    ii. Prediction of long-term risk of NTD in non-pregnant individuals.
    iii. Unresolved cases of anaemia.

For more information, contact your local Ampath representative.

REFERENCES

1. Naveed K, et al. 2023. Defining ferritin clinical decision limits to improve diagnosis and treatment of iron deficiency: A modified Delphi study. International Journal of Laboratory Hematology 45:377–386. DOI: 10.1111/ijlh.14016.
2. Simmonds WM, et al. 2024. Guidance for the gastrointestinal evaluation and management of iron deficiency in sub-Saharan Africa. South African Medical Journal 114(1b):e711. Available at https://doi.org/10.7196/SAMJ.2024.v114i1b.711.
3. Means RT, Fairfield KM. n.d. Clinical manifestations and diagnosis of vitamin B12 and folate deficiency. In: UpToDate, Takemoto CM (Ed), UpToDate, Waltham, MA. (Accessed on 6 November 2024).
4. Farrell CL, Kirsch SH, Hermann M. 2013. Red cell or serum folate: What to do in clinical practice? Clinical Chemistry and Laboratory Medicine 51(3): 555–569.