



An approach to anaemia diagnosis – concerns in primary care

To the Editor: The approach to the diagnosis of anaemia^[1] is a welcome addition to management of a common problem. A more nuanced approach may be warranted in primary care, where iron deficiency anaemia (IDA)^[2] and anaemia of chronic disease (ACD) are common.^[3,4] Iron administration is potentially deleterious in ACD associated with HIV^[5] and tuberculosis (TB).^[6]

Morphological v. biochemical approach

The diagnostic algorithm^[1] reflects a contemporary morphological approach to anaemia utilising the reticulocyte response and mean corpuscular volume (MCV) as the starting point for evaluation.^[7] Additionally, Alli *et al.*^[1] propose that a blood film be done on all patients, but provide no evidence to support the diagnostic yield of this approach. In their algorithm for investigation of anaemia in HIV infection in southern Africa, Van den Berg *et al.*^[8] do not advocate a blood film as routine. Nairz *et al.*^[9] suggest that a blood film would be indicated primarily to diagnose conditions where there is an increased reticulocyte production index (RPI) or macrocytosis with a low RPI. Limiting the performance of smears would ensure that it is done when it is most useful, and reduce costs and laboratory workload.

Assessment of red cell distribution width (RDW) was not discussed, but RDW can assist with diagnosis, generally being raised in IDA, vitamin B₁₂ and folate deficiency and bone marrow disorders and normal in liver disease and alcohol use.^[10]

A second approach to anaemia is the use of biochemical tests as a starting point.^[11,12] Reasons for this approach include the high prevalence of IDA and ACD, and the findings that up to 40% of patients with IDA can have a normal MCV,^[13] that patients with dimorphic anaemia from combined nutritional deficiencies can also have a normal MCV, and that clinically important vitamin B₁₂ deficiency can cause anaemia with a normal MCV.^[14,15]

A third approach is to combine biochemical testing (ferritin, vitamin B₁₂ and folate) with morphological red blood cell indices for all patients.^[8] There is no clarity on which approach is best in primary care. The third approach may be preferred in South Africa (SA), where nutrient deficiencies are common in females of reproductive age, e.g. a 15% prevalence of iron deficiency,^[2] a 1.9% prevalence of folate deficiency and an 8.8% prevalence of vitamin B₁₂ deficiency.^[16]

Diagnosis of iron deficiency anaemia

In the absence of inflammation, ferritin is the most sensitive, specific and cost-effective test for iron deficiency^[17,18] and can be used alone for confirmation.^[19] However, while a ferritin level of ≤ 15 $\mu\text{g/L}$ is very specific for iron deficiency, iron deficiency can only be ruled out when the ferritin level is >100 $\mu\text{g/L}$.^[17] In adults with a ferritin level of 35 - 44 $\mu\text{g/L}$, the positive likelihood ratio for iron deficiency is 1.83.^[20] It may be appropriate to rule out unsuspected inflammation by measurement of C-reactive protein.^[21]

Diagnosis of anaemia of chronic disease

The diagnosis is currently one of exclusion.^[17] As ferritin levels increase with inflammation, it can be difficult to differentiate between IDA and ACD, particularly when they coexist.^[18] The ferritin level for ruling out iron deficiency depends on the disease. In heart failure, iron deficiency can be diagnosed if the ferritin level is <100 $\mu\text{g/L}$, or <300 $\mu\text{g/L}$ with transferrin saturation (TSAT) $<20\%$.^[22] In chronic kidney disease, iron deficiency can be diagnosed if ferritin is <100 $\mu\text{g/L}$, or <200 $\mu\text{g/L}$ with TSAT $<20\%$.^[23]

Currently, National Health Laboratory Service (NHLS) reports give a normal range of ferritin of 13 - 150 $\mu\text{g/L}$ for adult women and 30 - 400 $\mu\text{g/L}$ for adult men. If clinicians use the lower limit of ferritin to exclude IDA in patients with or without inflammation, many patients with IDA will be untreated. It would assist generalists to have NHLS report ranges with narrative guidance.

Newer tests such as soluble transferrin receptor (sTfR), sTfR/log ferritin ratio, hepcidin, percentage of hypochromic red blood cells (%HRC) and reticulocyte haemoglobin content (CHr) can distinguish ACD from IDA, and can identify combined ACD and IDA.^[9,12] sTfR is performed in the NHLS. %HRC and CHr are automatically calculated during full blood count analysis by some automated analysers available in the NHLS, but laboratory information systems may not be configured to extract the results. Guidelines should be available on the use of these tests in the public health sector.

TB as a cause of anaemia in patients with HIV

TB is the most common cause of moderate or severe anaemia in patients with HIV.^[15,24] Current National Department of Health guidelines^[25] recommend ruling out TB in patients with severe anaemia (haemoglobin concentration <8 g/dL^[26]) and HIV infection and no clear cause, but do not specify which investigations to do. Extrapulmonary TB is as common as pulmonary TB in these patients,^[27] so in addition to a chest radiograph and sputum Xpert MTB/RIF assay, it is important to consider an ultrasound scan of the abdomen, pericardium and lower chest.^[28] In a recent series of 50 patients with severe anaemia and HIV infection in Mthatha, SA, 86% had clinical and/or bacteriologically confirmed and previously undiagnosed TB.^[29]

More research is needed into the prevalence and causes of anaemia in primary care in SA as well as performance characteristics of tests for anaemia, to inform a context-specific evidence-based diagnostic approach to this condition.

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