The straight and marrow - a primary care approach to anaemia

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Abstract

Anaemia remains a common global health issue with approximately a quarter of the world’s population affected despite universal initiatives to address the disorder. Iron deficiency anaemia and anaemia of chronic disease remain the two top ranking causes of anaemia globally and when these conditions co-exist, diagnosis is often challenging. In South Africa, high-risk groups include children, pregnant women and human immunodeficiency virus infected individuals. The morbidity and mortality associated with anaemia mandates the correct identification of the underlying cause, thus ensuring early, appropriate management. This review proposes morphological assessment with the appropriate baseline biochemical testing as the initial approach to unexplained anaemia in a primary health care setting in South Africa, in order to expedite diagnosis and ensure appropriate management.

Keywords: anaemia, anaemia, anaemia diagnosis, anaemia of chronic disease, human immunodeficiency virus infection, iron deficiency anaemia

Introduction

Anaemia can be defined as a reduction in the haemoglobin concentration of circulating red blood cells. Normal haemoglobin concentration thresholds differ based on the gender, age and physiological status (e.g. pregnancy) of the patient. The World Health Organization (WHO) grades the severity of anaemia within these groups as follows:

<table>
<thead>
<tr>
<th>Patient demographic</th>
<th>Mild anaemia</th>
<th>Moderate anaemia</th>
<th>Severe anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult men</td>
<td>11-12.9 g/dL</td>
<td>8-10.9 g/dL</td>
<td>&lt; 8 g/dL</td>
</tr>
<tr>
<td>Adult women (non-pregnant)</td>
<td>11-11.9 g/dL</td>
<td>8-10.9 g/dL</td>
<td>&lt; 8 g/dL</td>
</tr>
<tr>
<td>Adult women (pregnant)</td>
<td>10-10.9 g/dL</td>
<td>7-9.9 g/dL</td>
<td>&lt; 7 g/dL</td>
</tr>
<tr>
<td>Children: 6-59 months</td>
<td>10-10.9 g/dL</td>
<td>7-9.9 g/dL</td>
<td>&lt; 7 g/dL</td>
</tr>
<tr>
<td>Children: 5-11 years</td>
<td>11-11.9 g/dL</td>
<td>8-10.9 g/dL</td>
<td>&lt; 8 g/dL</td>
</tr>
<tr>
<td>Children: 12-14 years</td>
<td>11-11.9 g/dL</td>
<td>8-10.9 g/dL</td>
<td>&lt; 8 g/dL</td>
</tr>
</tbody>
</table>

Anaemia is one of the most common haematological problems encountered in primary clinical practice today and is an indicator of either poor nutrition or poor health. The WHO estimates the South African prevalence of anaemia in those at highest risk, namely pre-school children and pregnant women, at 41% and 30% respectively.

Anaemia occurs either due to decreased bone marrow production of red blood cells or peripheral loss/destruction of circulating red blood cells. The former can be due to nutritional deficiencies, anaemia of chronic disease (ACD) or inherited bone marrow disorders whereas the latter can be due to blood loss, haemolysis or splenic sequestration. In practice however, the aetiology of anaemia is often multifactorial and diagnosis therefore requires a structured approach.

This article is by no means a comprehensive overview of anaemia but rather attempts to address some of the common causes of anaemia in the South African primary health care setting and to provide guidance with respect to some of the basic laboratory investigations that could be requested to differentiate between these causes.

Iron deficiency anaemia

Iron deficiency is the most common cause of anaemia globally, accounting for > 50% of all cases. Increased iron requirements during growth and pregnancy make children and pregnant women especially susceptible. Iron deficiency anaemia (IDA) can also be due to insufficient dietary intake, chronic blood loss from the urogenital or gastrointestinal systems or malabsorption. Weakness, fatigue and poor concentration are non-specific clinical features and in fact, because of the chronicity of IDA, many patients may be asymptomatic. Iron deficiency may increase susceptibility to infection and precipitate heart failure.

Iron deficiency has significant consequences for the cognitive and physical development of children and is an important contributor to newborn and maternal mortality. IDA typically results in a hypochromic microcytic anaemia which can be mild to severe.

Anaemia of chronic disease

ACD is the second most common cause of anaemia after IDA. Differentiating between these two causes of anaemia is a common diagnostic challenge in primary practice. Conditions
The straight and marrow - a primary care approach to anaemia

most commonly associated with ACD include infections such as human immunodeficiency virus (HIV) and tuberculosis, cancer, rheumatoid arthritis and other auto-immune conditions as well as chronic renal impairment. ACD is typically associated with a mild to moderate, normocytic anaemia.5

**Megaloblastic anaemia**

A deficiency of either Vitamin B₁₂ or folate results in ineffective haematopoiesis and consequently megaloblastic anaemia. The mean cell volume (MCV) is typically raised with oval macrocytes, tear drop cells, hypersegmented neutrophils and giant metamyelocytes present on peripheral blood smear (PBS) examination.6 This picture may however be complicated if a co-existing iron deficiency is present (i.e. mixed deficiency anaemia) resulting in normalisation of the MCV. The commonest cause of megaloblastic anaemia is Vitamin B₁₂ deficiency which often results from immune mediated destruction of parietal cells of the stomach and/or intrinsic factor (i.e. pernicious anaemia).7

**Anaemia in pregnancy**

Anaemia is a major cause of maternal and perinatal morbidity and mortality and therefore warrants early diagnosis and management. The primary aetiologies underpinning anaemia in pregnancy in low- and middle-income countries are nutritional deficiencies, most commonly IDA, infectious diseases such as malaria and untreated haemoglobinopathies.8 HIV infection and parasitic infestations have been shown to be significant contributors to the disease burden of anaemia in South African pregnant women.9 The incidence of anaemia in HIV infected pregnant women is significantly increased 10 and early antenatal testing is therefore essential.11

**Anaemia in paediatrics**

South Africa has a high prevalence of anaemia in both pre-school and school-aged children. Several independent studies have reported the incidence of anaemia in this population group as ranging from 22% to 57% 12,13,14 which is in stark contrast to the 10.7% stated in the South African National Health and Nutrition Examination Survey (SANHANES-1) report.15 Nutritional deficiencies and malaria have been reported as major causes of childhood anaemia in sub-Saharan Africa.16 High levels of poverty, food insecurity and infectious diseases are also major contributors and anaemia in childhood is often associated with parasitic infestations such as hookworm.16

**Anaemia and HIV infection**

Approximately 95% of HIV-infected patients will be diagnosed with anaemia during the course of their disease17 with the degree of anaemia corresponding to disease progression.18 The cause of anaemia in these patients is often multifactorial.18 Nutritional deficiencies should be excluded in all HIV-positive patients with anaemia19 as the MCV can be unreliable in patients on antiretroviral therapy (ART). Zidovudine (AZT) therapy, especially when used as a single agent, has been associated with anaemia in the first six months following initiation of treatment as well as a dose dependent macrocytosis.20 Opportunistic infections, such as tuberculosis and parvovirus B19, as well as secondary malignancies are important causes of anaemia in immunosuppressed patients and therefore need to be actively excluded in all HIV positive patients with severe anaemia. A bone marrow investigation should be considered, especially if the full blood count (FBC) shows additional unexplained abnormalities.19 HIV infection increases the risk of serious haemolytic anaemias, such as thrombotic thrombocytopenic purpura,21 and a request for PBS analysis for red cell fragments should be requested in all cases presenting with anaemia and thrombocytopenia.

**The basic laboratory work-up of anaemia**

Anaemia is not a diagnosis20 and will therefore always require further investigation to determine the cause if not immediately clinically evident. A thorough clinical history and physical

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**Figure 1.** A basic approach to the first-line investigations in anaemia in primary practice. In all cases, once a nutritional deficiency has been confirmed, the cause of the nutritional deficiency should be investigated.
examination is essential and can direct the type and urgency of further investigations.

A morphological approach to the investigation of anaemia is advocated. This approach utilises the red cell indices, specifically the MCV, to differentiate between causes of anaemia. As the MCV is routinely performed on all full blood counts (FBCs), this approach is both cost-effective and practical. In any patient with clinical features suggestive of anaemia, biochemical testing for serum ferritin, vitamin B₁₂ and folate should be considered as baseline tests as the occurrence of these deficiencies in South Africa is common.²² A basic interpretation of these investigations is outlined in the algorithm in Figure 1.

**Other useful diagnostic aids:**

**The red cell distribution width (RDW)**

The RDW is a measure of variation in the size of the red blood cells and is routinely reported on the FBC. A raised RDW is associated with iron deficiency anaemia and megaloblastic anaemia (vitamin B₁₂ and/or folate deficiency) and can be used to differentiate these from other causes of a microcytic (e.g. thalassaemia) and macrocytic anaemia (e.g. liver disease) respectively.²²

**The Mentzer index**

The Mentzer index can be useful in distinguishing between IDA and β-thalassaemia trait, where a value of less than 13 (obtained by dividing the MCV by the red cell count (RCC)) favours a diagnosis of β-thalassaemia trait.

**Peripheral blood smear (PBS) examination**

Examination of the PBS remains a crucial, relatively inexpensive diagnostic aid in patients with anaemia. It is especially useful in patients with macrocytic anaemias, haemolytic anaemias, suspected haemoglobinopathies and malaria infection and can guide further appropriate testing.⁶,²³

**Reticulocyte count**

The reticulocyte count provides insight into bone marrow red cell production and is useful in differentiating between inadequate production and blood loss/premature red cell destruction. The reticulocyte production index (RPI) is a calculated value that reflects the bone marrow response relative to the degree of anaemia. A reduced RPI is indicative of an inadequate bone marrow response for the degree of anaemia present.⁵

**Differentiating between IDA and ACD**

The biochemical iron profile is the most useful investigation to differentiate between IDA and ACD. A serum ferritin of < 30 ng/ml provides a 92–98% positive predictive value for IDA.⁵ Ferritin is an acute phase reactant and a normal level therefore does not exclude an underlying IDA. A high ferritin is typically associated with ACD and markers of inflammation such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can be utilised to confirm the presence of a chronic inflammatory condition. A ferritin level of > 100 µg/L can generally be used to rule out IDA.²⁴ Serum iron levels will be reduced in both IDA and ACD and is therefore not useful in distinguishing between these two conditions. Serum transferrin can however be useful as levels are usually reduced/normal in ACD but increased in IDA. Empiric iron supplementation should be avoided in uncertain situations as it can have adverse consequences.⁵

### Table 2. Results of biochemical investigations in IDA vs ACD

<table>
<thead>
<tr>
<th></th>
<th>IDA</th>
<th>ACD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Transferrin level</td>
<td>Raised</td>
<td>Reduced/normal</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>Reduced</td>
<td>Normal/raised</td>
</tr>
</tbody>
</table>

**Investigating for megaloblastic anaemia**

Megaloblastic anaemia will be confirmed by a low serum vitamin B₁₂ or serum folate level. A serum vitamin B₁₂ threshold of 148 pmol/L has shown 97% sensitivity for detecting true deficiency. Serum folate has shown equal diagnostic capability to red cell folate but is less cumbersome. A serum folate level of less than 7 nmol/L is diagnostic. When borderline/low normal vitamin B₁₂ or folate levels are obtained in a patient with strong clinical suspicion of megaloblastic anaemia, second-line testing such as plasma methylmalonic acid and homocysteine can be performed. Treatment should however not be delayed in these situations to avoid irreversible neurological impairment.²⁵

### Table 3. Results of biochemical investigations in vitamin B₁₂ vs folate deficiency

<table>
<thead>
<tr>
<th></th>
<th>Vitamin B₁₂ deficiency</th>
<th>Folate deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum vitamin B₁₂</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum folate</td>
<td>Normal</td>
<td>Reduced</td>
</tr>
<tr>
<td>Plasma methylmalonic acid</td>
<td>Raised</td>
<td>Normal</td>
</tr>
<tr>
<td>Plasma homocysteine</td>
<td>Raised</td>
<td>Raised</td>
</tr>
</tbody>
</table>

**Conclusion**

Anaemia can result from a wide range of conditions, often with multiple mechanisms at play. Prompt identification of the cause of the anaemia is critical for appropriate management of patients. The value of a comprehensive history and scrupulous physical examination should not be underestimated in directing further rational investigation of the cause of the anaemia.

**References**