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: anemia, 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.[1] 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 1. The WHO defining thresholds and grading of anaemia[2]

Patient demographic	Mild anaemia	Moderate anaemia	Severe anaemia
Adult men	11-12.9 g/dL	8-10.9 g/dL	< 8 g/dL
Adult women (non-pregnant)	11-11.9 g/dL	8-10.9 g/dL	< 8 g/dL
Adult women (pregnant)	10-10.9 g/dL	7-9.9 g/dL	< 7 g/dL
Children: 6-59 months	10-10.9 g/dL	7-9.9 g/dL	< 7 g/dL
Children: 5-11 years	11-11.4 g/dL	8-10.9 g/dL	< 8 g/dL
Children: 12-14 years	11-11.9 g/dL	8-10.9 g/dL	< 8 g/dL

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.[2] 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.[1]

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.[3]

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.[2] 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.[4] Iron deficiency has significant consequences for the cognitive and physical development of children and is an important contributor to newborn and maternal mortality.[2] IDA typically results in a hypochromic microcytic anaemia which can be mild to severe.[4]

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

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 B_{12} 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 B_{12} 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 disease[17] 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 anaemia[19] 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 diagnosis[20] and will therefore always require further investigation to determine the cause if not immediately clinically evident. A thorough clinical history and physical
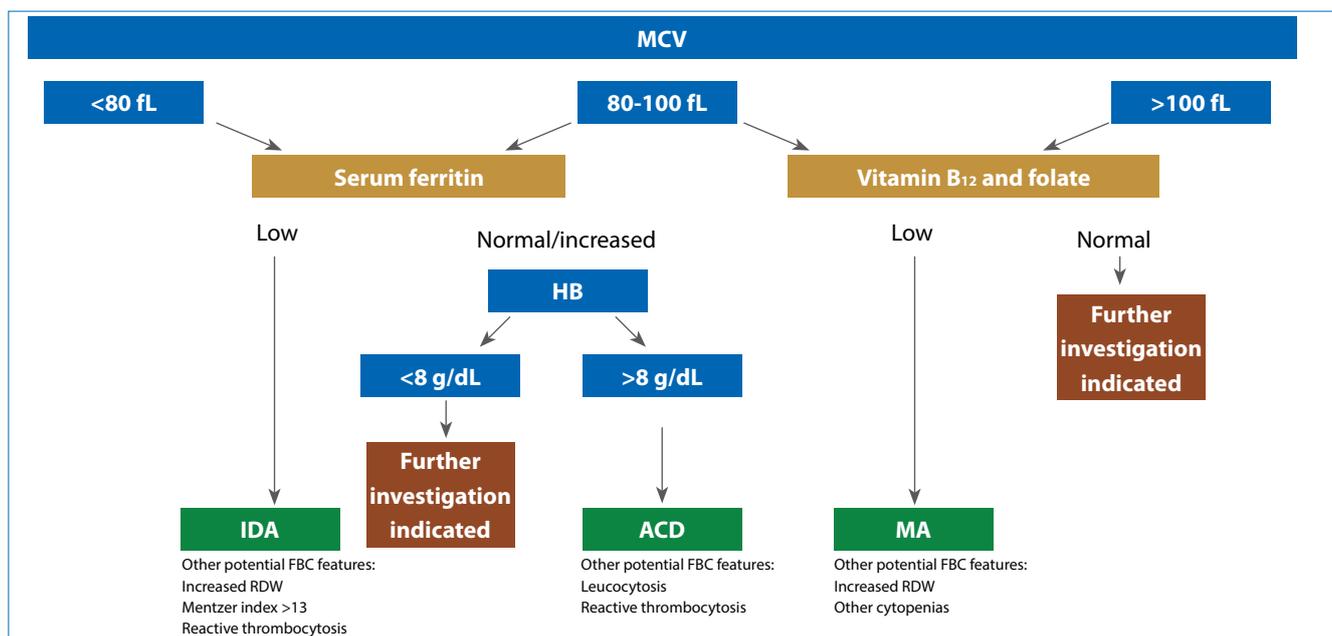

Figure 1. A basic approach to the first-line investigations in anaemia in primary practice. In all cases, once a nutritional deficiency has been confirmed, the cause of the nutritional deficiency should be investigated.

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 B$_{12}$ and folate should be considered as baseline tests as the occurrence of these deficiencies in South Africa is common.[15] 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 B$_{12}$ 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.[3]

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

	IDA	ACD
Serum iron	Reduced	Reduced
Transferrin level	Raised	Reduced/normal
Transferrin saturation	Reduced	Reduced
Serum ferritin	Reduced	Normal/raised

Investigating for megaloblastic anaemia

Megaloblastic anaemia will be confirmed by a low serum vitamin B$_{12}$ or serum folate level. A serum vitamin B$_{12}$ 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 B$_{12}$ 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

	Vitamin B12 deficiency	Folate deficiency
Serum vitamin B12	Reduced	Normal
Serum folate	Normal	Reduced
Plasma methylmalonic acid	Raised	Normal
Plasma homocysteine	Raised	Raised

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

1. World Health Organization. The global prevalence of anaemia in 2011. Geneva: WHO; 2015.

2. WHO. De Benoist B, McLean E, Egli I, Cogswell M, eds. Worldwide Prevalence of Anaemia 1993–2005. Geneva, Switzerland, 2008.

3. Alli N, Vaughan J, Patel M. Anaemia: Approach to diagnosis. S Afr Med J. Jan 2017;101(1):2327.

4. Camaschella C. Iron-Deficiency Anemia. N Engl J Med. 7 May 2015;372(19):1832-43.

5. Weiss G, Goodnough LT. Anemia of Chronic Disease. N Engl J Med. 10 Mar 2005;352(10):1011-23.

6. Bain BJ. Diagnosis from the Blood Smear. N Engl J Med. 4 Aug 2005;353(5):498-507.

7. Nagao T, Hirokawa M. Diagnosis and treatment of macrocytic anemias in adults. J Gen Fam Med. 2017;18:200-4.

8. Rahman MM, Abe SK, Rahman MS, Kanda M, Narita S, Bilano V, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. Am J Clin Nutr. 2016;103:495-504.

9. Hoque M, Hoque E, Kader SB. Risk factors for anaemia in pregnancy in rural KwaZulu-Natal, South Africa: Implication for health education and health promotion. SA Fam Pract. 2009;51(1):68-72.

10. Tunkyi K, Moodley J. Prevalence of anaemia in pregnancy in a regional health facility in South Africa. S Afr Med J. Jan 2016;106(1):101-4.

11. Tunkyi K, Moodley J. Anaemia in pregnancy in a setting of high HIV prevalence rates. S Afr J Infect Dis. 2017;32(4):138-41.

12. Gwetu TP, Chhagan M, Craib M, Taylor M, Kauchali S. Persistent and new-onset anaemia in children aged 6 – 8 years from KwaZulu-Natal Province, South Africa. S Afr J Child Health. 2015;9(4):127-9.

13. Mamabolo RL, Alberts M. Prevalence of anaemia and its associated factors in African children at one and three years residing in the Capricon District of Limpopo Province, South Africa. Curationis. 2014;37(1):1-9.

14. Wege MH. A retrospective review of the prevalence and management of anaemia in children at Red Cross War Memorial Children's Hospital [dissertation]. University of Cape Town; 2015.

15. Shisana O, Labadarios D, Simbayi L, Rehle, T, Zuma K, Parker W, et al. The South African National Health and Nutrition Examination Survey (SANHANES-1). Cape Town: HSRC Press; 2013. 423 p.

16. Thejpal R. Iron deficiency in children. S Afr Med J. Jul 2015;105(7):607.

17. Baker K. The hematologic complications of HIV infection. ASH Education Program. 2003;1:299.

18. Redig AJ, Berliner N. Pathogenesis and clinical implications of HIV-related anemia in 2013. Hematol. 2013;377-81.

19. Opie J. Haematological complications of HIV infection. S Afr Med J. Jun 2012;102(6):465-8.

20. Van den Berg K, van Hasselt J, Bloch E, Crookes R, Kelley J, Berger J, et al. A review of the use of blood and blood products in HIV-infected patients. S Afr J HIV Med. Jun 2012;13(2):87-104.

21. Kaushansky K, Lichtman MA, Prchal JT, Levi MM, Press OW, Burns LJ, et al. Williams Haematology. 9th ed. McGraw-Hill Education: United States of America; 2016.

22. AlDallal S. Iron Deficiency Anaemia: A Short Review. J Immunooncol. 26 Aug 2016 ;2(1):1-6.

23. Adewoyin AS, Nwogoh. Peripheral blood film – A review. Ann Ibd Pg Med. Dec 2014;12(2):71-9

24. DeLoughery TG. Microcytic anemia. N Engl J Med. 2 Oct 2014;371(14):1324-31.

25. Devalia V, Hamilton MS, Molloy AM. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 18 Jun 2014;166:496-513.