AMPATHCHAT no. 85

TO ACT OR NOT? CHANGES TO ADULT FBC REFERENCE INTERVALS EXPLAINED

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KEY MESSAGES

- Reference intervals should be compliant with national and international laboratory standards and should be representative of the population, taking racial diversity into account.
- FBC results should always be interpreted in the context of the patient's clinical picture.
- Do not hesitate to contact an Ampath pathologist for advice, if required.

INTRODUCTION

In June 2023, Ampath adopted a new set of reference intervals applicable to Full Blood Counts (FBCs) performed on adults. The rationale for the change was to ensure that reference intervals are as representative as possible of our diverse South African population whilst continuing to comply with local and international standards, namely South African National Accreditation System (SANAS)[1] and Clinical and Laboratory Standards Institute (CLSI).[2]

REFERENCE INTERVALS ADOPTED BY AMPATH

The reference intervals adopted by Ampath were established by Dr Koker et al,[3] in a South African study conducted in the Western Cape in accordance with CLSI guidelines.[2] Study participants included healthy adults who presented for first time blood donation. Stringent screening of participants was performed by means of a pre-blood donation questionnaire, assessment of vital signs and testing for HIV, Hepatitis B, Hepatitis C and syphilis. In addition, individuals with iron deficiency (serum ferritin below reference limit) or with red cell indices suggestive of thalassaemia trait were excluded. The study included 409 female and 253 male participants with representation of all major race groups. These reference intervals were successfully verified by Ampath through comparison with at least 20 male and 20 female individuals.

DEFINITION OF REFERENCE INTERVAL AND RELATED TERMINOLOGY AND IMPLICATIONS FOR CLINICAL PRACTICE

The CLSI defines a reference interval as 'the interval between, and including, two reference limits'. A reference value is defined as 'a value obtained by measurement' on a reference individual (reference study participant).[2] It is common practice, as with our newly adopted reference intervals, for reference intervals to represent the central 95% of all reference values obtained. The implication of this is that 5% of healthy individuals may have results that fall outside the reference interval (above or below). Results must therefore always be interpreted in the context of the clinical picture.

SUGGESTED ACTIONABLE FBC RESULTS

There are several sources that describe 'normal' FBC parameters in adults. The World Health Organization (WHO) Classification of Haematolymphoid Tumours[4,5] and The International Consensus Classification (ICC) of myeloid neoplasms and acute leukemias[6] each provide their own diagnostic criteria with corresponding FBC parameter cut-offs. These criteria and cut-offs are applicable to certain haematological pre-malignant and malignant diseases (e.g. clonal haematopoiesis, myelodysplastic syndrome/neoplasm and myeloproliferative neoplasm).

For consideration, some of the definitions provided by the WHO, the ICC and William's Hematology, 10th edition are presented in the table below.[4,5,6] The WHO diagnostic criteria are more widely used in South Africa and a transition from the WHO 4th to the 5th edition classification can be expected. Bear in mind that results outside of the cut-off values presented in the table are not necessarily indicative of pathology. Rather it indicates that pathology is possible and further testing should be considered taking into account the clinical presentation.

TABLE 1: DEFINITIONS APPLICABLE TO ADULT FBC PARAMETERS

	Definition	Source and comment
Anaemia	Haemoglobin <13 g/dL in men and <12 g/dL in women	WHO 5th ed. and ICC. Note the change from WHO 4th ed. where anaemia was defined as haemoglobin of <10 g/dL for men and women.
Classification of anaemia by mean corpuscular volume (MCV)	Normocytic anaemia: MCV 80–100 fL Macrocytic anaemia: MCV >100 fL Microcytic anaemia: MCV <80 fL	Williams, 10th ed.
Polycythaemia	Haemoglobin >16.5 g/dL in men and >16.0 g/dL in women. Or haematocrit of >49% in men and >48% in women.	WHO 4th ed., WHO 5th ed. and ICC.
Leucocytosis	White cell count ≥11 x 10^9/L	WHO 4th ed., WHO 5th ed. and ICC.
Neutropenia	Absolute neutrophil count <1.8 ×10^9/L	WHO 4th ed., WHO 5th ed., ICC and Williams 10th ed.
Neutrophilia	>7.5 × 10^9/L	Williams 10th ed.
Lymphopenia	Lymphocyte count <1.0 × 10^9/L	Williams 10th ed.
Lymphocytosis	Lymphocyte count >4 × 10^9/L	Williams 10th ed.
Eosinophilia	≥0.5 × 10^9/L	Williams 10th ed. Note that persistent, unexplained eosinophilia of >1.5 × 10^9/L, warrants further investigation to exclude clonal disease (as per WHO 4th ed., WHO 5th ed. and ICC criteria).
Monocytosis	Monocyte count ≥1 x 10^9/L	WHO 4th ed., WHO 5th ed., and ICC.
Thrombocytopenia	Platelet count <150 ×10^9/L	WHO 5th ed., ICC and Williams 10th ed. Note the change from WHO 4th ed. where thrombocytopenia was defined as platelet count <100 x 10^9/L.
Thrombocytosis	Platelet count ≥450 x 10^9/L	WHO 4th ed., WHO 5th ed. and ICC.

Abbreviations:

- WHO 4th ed.: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J et al. eds. WHO classification of tumours of haematopoetic and lymphoid tissues. 4th ed. Lyon: International Agency for Research on Cancer (IARC), 2008
- WHO 5th ed.: Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022; 36(7):1703-1719. doi: 10.1038/s41375-022-01613-1.
- ICC : Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228. doi:10.1182/blood.2022015850
- Williams, 10th ed.: Kaushansky K, Prchal JT, Burns LJ, Lichtman MA, Levi M, Linch DC. eds. Williams Hematology, 10e. McGraw Hill; 2021.

The FBC should always be interpreted in the context of the patient's history (including presenting complaint and drug/toxin exposure), examination findings and trend compared to previous results. Some examples of normal variations include an expected increase in MCV during pregnancy and a lower than usual neutrophil count in some individuals of sub-Saharan African descent (benign ethnic neutropenia).[8,9]

Suggested triggers for consultation with a pathologist include:

- Persistent, unexplained FBC abnormalities.
- Symptomatic cytopenias (e.g. febrile neutropenia, anaemia with haemodynamic compromise, symptomatic thrombocytopenia).
- Symptoms of hyperviscosity secondary to high cell counts.
- Clinical suspicion of a haematological disorder.

At Ampath, every FBC with parameters that fall outside of the reference interval is screened by senior technologists and/or a pathologist in conjunction with the patient's previous results. Blood film examination is performed in accordance with standard operating procedures and includes clinical suggestions when necessary. When in doubt, please feel free to contact one of our pathologists for advice.

REFERENCES

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