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Review Article

A critical review on the assurance of accuracy in automated complete blood count test reports by rectification of spuriously elevated MCHC values

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ABSTRACT

Spuriously elevated or decreased results are encountered frequently in hematology analysers in various parameters of the complete blood count (CBC). These results can be either true reflections of patient's disease or may be spurious findings due to multiple pre- analytical factors. It is necessary to review these spurious results and perform necessary corrective actions before issuing the final report to the patient. Correction of spurious results ensures accuracy of the patient results and thereby helps the clinicians in providing optimal diagnosis and treatment to the patients. In this study, the predominant focus is on mean corpuscular haemoglobin concentration (MCHC) elevation which is derived as a calculation from haemoglobin and haematocrit values. As a result, it can be affected by preanalytical, postanalytical or analytical factors. In literature there are only a few articles related to correction of spuriously high MCHC. This article reviews most important studies available in literature on correction of spuriously high MCHC.

Keywords: Automated complete blood count, Report accuracy, Spuriously elevated MCHC

INTRODUCTION

Automated/semiautomated hematology analyzers are utilized by clinical hematology laboratories to obtain accurate, precise and quick complete blood count (CBC) results on EDTA-anticoagulated whole blood specimens. The components of the CBC can help identify a wide range of pathologies and remain one of the most ordered and useful tests in clinical medicine. While automated analyzers have allowed for fast and accurate results, spurious results may arise in several situations and with different parameters.[1] Fully automated hematology analyzers employ two principal methods of counting blood cells which are volumetric impedance and light-scatter technique. Both employ variations in the handling of samples before the count, such as automatic dilution and separation of samples into aliquots.[2] Advances in technology have resulted in hematology cell counters with improved resolution, increased accuracy and precision, wide dynamic range, minimal sample carryover and lesser turnaround time.[3] The standard CBC includes red cell count (RBC), haemoglobin (Hb), haematocrit (Hct), red cell indices (MCV, MCHC, MCH), platelet count, white cell count and differential counts. Newer machines, capable of calculating RDW or red cell morphology index, RBC-O, HGB-O, reticulocyte parameters, mean platelet volume and absolute differential counts are now being used in many clinical laboratories. MCV, MCH, and MCHC are termed red cell indices included in routine blood examination to define the size and haemoglobin content of red blood cells. MCV determines the size of red blood cells, MCH defines the amount of haemoglobin per

red blood cell, and MCHC indicates the amount of haemoglobin per unit volume.[4] The increased complexity

of these instruments, however, requires extensive training for the laboratory technologists with regards to instrument operation, maintenance, malfunction, as well as the interpretation of patient and quality control data. Although laboratory personnel are quick to suspect spurious results, there are many reasons for these false results, which can be related to the patient clinical condition, blood sampling technique or analyzer performance related issues.[5]

SIGNIFICANCE OF MCHC IN HEMATOLOGY ANALYZERS

Mean corpuscular haemoglobin concentration (MCHC) is one of the key parameters in complete blood counts, providing vital information about haemoglobin concentration in red blood cells. The normal values for MCHC are 33.0±1.5 g/dl.[6] It is the average haemoglobin concentration per RBC, in grams/dl. In automated hematology analyzers it is calculated from the haemoglobin and the haematocrit. On many automated instruments, the MCHC is one of the most useful parameters to ensure accuracy of the red cell parameters in individual patient samples. In daily practice in hematology laboratories, spuriously increased MCHC induces an analytical alarm or "flag" and needs prompt corrective action to ensure delivery of the right results to the clinician.[7]

Mean corpuscular haemoglobin concentration (MCHC) is often used together with mean corpuscular volume (MCV) and mean corpuscular haemoglobin content (MCH) as diagnostic indicators for anemia classification. It has important clinical value in early detection of the cause of anemia and the underlying etiology of anemia. Therefore, the accuracy of MCHC results is of great significance for the diagnosis and treatment of diseases.[8] Persistently high MCHC in all the blood samples tested over a time should be investigated for causes like analyzer malfunction.[9] Spurious data may be due to instrument malfunction or to problems with the blood sample itself.[10] In fact, different etiologies lead to spurious results of CBC analysis, of which the most common ones are the interferents including cold agglutinins, hemolysis and lipemia.[11]

FLAGGING IN HEMATOLOGY ANALYZERS

Automated hematology analyzers exhibit alerts or flags when abnormalities are encountered in patient samples. In general following are some of the flags/ suggestions to detect spurious CBC results.[7]

Automated or manual review of analyzer-generated flags. Some of the flags include RBC Agglut. Turbidity/HGB Interf, etc. Histograms (RBC count, PLT, and WBC count if available), and scattergrams (WBC count DIFF). Automated or manual review of delta check failures. Automated or manual review of the analyzer generated results. Hb and Hct discrepancy or failure of one or more of the so-called "three rules of three".

Hct ≈ Hb×3 (often referred to as the Hct and Hb rule), Hb ≈ RBC×3 (Hb and RBC rule), RBC ≈ Hb÷3 (RBC and Hb rule).

Elevated MCHC, typically >36.5 g/dl or >365 g/l, but the elevation threshold may vary with the analyzer. Decreased MCHC, typically <28 g/dl or <280 g/l, but the threshold may vary with the analyzer. Visual inspection of the settled or spun blood specimen tube for lipemia, hemolysis, and icterus. Blood smear examination for the validation of automated results to look for spherocytes, stomatocytes, nucleated RBCs, agglutination etc. For spuriously elevated MCHC which is the focus on this review document, usual flags/ suggestions by the analyzer are RBC Agglutination Turbidity interf, MCHC alarm. Since MCHC is a calculated parameter, different etiologies responsible for spurious results in HGB, RBC, HCT can cause spuriously elevated values in MCHC. Abnormalities can be attributed to either red cells or to the presence of abnormalities in plasma.

Red cell abnormalities

True elevation of MCHC is a rare phenomenon and can be seen in case of hereditary spherocytosis, xerocytosis, autoimmune hemolytic anemia rare haemoglobinopathies like homozygous sickle cell disease, HbC disease etc. Examination of peripheral smear along with osmotic fragility test, genetic testing, HPLC can further aid in confirmation of diagnosis.[12-14]

Cold agglutinin disease

Cold agglutinin disease is the most common cause of spuriously elevated MCHC due to red cell causes. Cold agglutinins may be seen with the primary cold agglutinin disease CAD in the absence of an underlying disorder or secondary cold agglutinin syndrome secondary to infections, autoimmune disorders, or overt lymphoma.[15]

The presence of cold agglutinins (CAs) in samples intended for complete blood count (CBC) using automated hematology analyzers might cause serious preanalytical errors in erythrocytes at a temperature below 37 °C.[16] Cold agglutinin disease is a type of autoimmune hemolytic anemia (AIHA) characterized by an immune reaction due to usually IgM antibodies directed against polysaccharide antigens located on RBC surface and evident at temperatures <37°C). The resulting antigen-antibody complex strongly activates the classical complement cascade, which might cause removal of RBCs in the reticuloendothelial system, intravascular and extravascular hemolysis.[17] A cold exposure or a concurrent infection may be sufficient cause for autoagglutination. In laboratory practice, presence of cold agglutinins may be detected on PS examination which will show presence of agglutination. The presence of cold agglutinins (CAs) in

samples intended for complete blood count (CBC) using automated hematology analyzers might cause serious preanalytical errors.[18] The analyzer shows decreased RBC counts, an untrue increase in cell volume and therefore spuriously elevated MCHC (more than 36.5). PS examination shows presence of agglutinated red cells. Among the various approaches recommended for obtaining reliable results, a common practice is to incubate the blood specimen at 37°C, typically for 10–15 min, and immediately rerun the analysis. In majority of the cases, the counts will be corrected. PS examination after incubation may reveal absence of agglutination.

Plasma abnormalities

Presence of lipemia, icterus or hemolysis can be responsible for elevated MCHC. Visual examination of spun or settled plasma will help to identify the cause of interference.

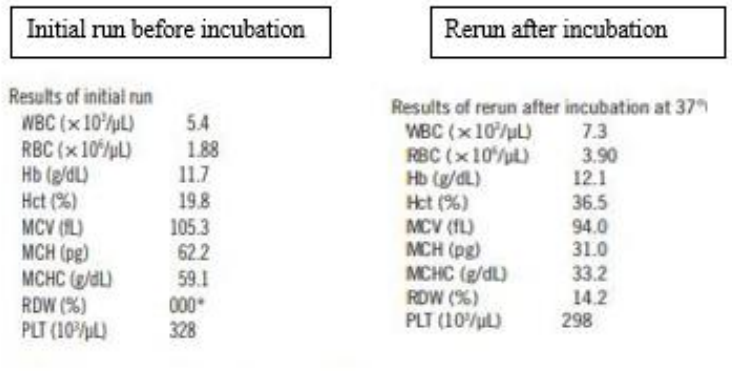

Figure 1: Complete blood count results in RBC agglutination before and after incubation.[7]

Lipemia

Lipemia or increased concentration of lipids (triglycerides consisting of chylomicrons and very-low-density lipoproteins) can be seen commonly in patient samples. Lipemia interferes primarily with Hb measurement and results in falsely higher Hb, MCH, and MCHC.[19] A discrepancy between Hb and Hct with a spurious elevation of MCHC can be seen. Analyzer may generate flag of turbidity or Hb interf is also helpful. Lipemic blood appears milky turbid upon visual inspection of the specimen after centrifugation or settling. In suspected lipemia cases, if 37°C incubation does not bring the RBC parameters in an appropriate range, procedures like plasma replacement should be done.[20]

PLASMA REPLACEMENT PROCEDURE

Blood is centrifuged at 3,500 rpm for 10 min. The level on the centrifuged specimen tube is marked manually and using a disposable pipette, maximum plasma is aspirated without disturbing the buffy coat and transferred to an empty tube. Equal volume of isotonic solution (the diluent used in the analyzer or normal saline) is added up to the level marked, mixed well and rerun.

The CBC results obtained from the rerun after plasma replacement are considered reliable if the WBC, RBC, and PLT counts match with those of the initial run (within between-run reproducibility limits). In case of a discrepancy between the rerun values and initial results of WBC, RBC, and/or PLT counts, the reliable results from the initial run (WBC, RBC, and PLT counts, Hct, MCV, and RDW) may be reported along with the rerun results of Hb, MCH, and MCHC.

Hemolysis

Another scenario in which spurious MCHC results seen is hemolysis. Since MCHC calculation involves haemoglobin, MCHC can be falsely elevated when haemoglobin is spuriously elevated.[21,22] Hemolysis may occur inside human body under pathological conditions, or in vitro after blood sample collection related to pre-analytical errors. Haemolyzed samples may produce unreliable results, leading to errors in diagnostic and monitoring evaluations.

Common causes of in vivo hemolysis include hereditary spherocytosis, autoimmune hemolytic anemia or severe sickle cell disease. Blood specimens from patients with in vivo hemolysis yield accurate automated CBC results but with higher-than-normal MCH and MCHC. PS examination in cases of in vivo hemolysis may show increased polychromasia and/or the presence of spherocytes, schistocytes, and/or sickle cells. Other supportive evidence may include increased unconjugated bilirubin, reticulocytosis, decreased or absent haptoglobin. Other confirmatory tests like osmotic fragility test, direct Coombs test may be advised.

On the other hand, in vitro hemolysis may be attributed to various pre-analytic factors like inappropriate specimen collection, storage, and/or transport conditions.[23] The indicators for in vitro hemolysis include normal reticulocyte count, increased level of serum potassium, lactate dehydrogenase, and AST concentrations. On

hematology analyzers, a false low RBC count and Hct concentration and false higher MCH and MCHC may be seen with disrupted 'rule of three". PS smear examination may show falsely elevated platelet count due to "ghost red cells".

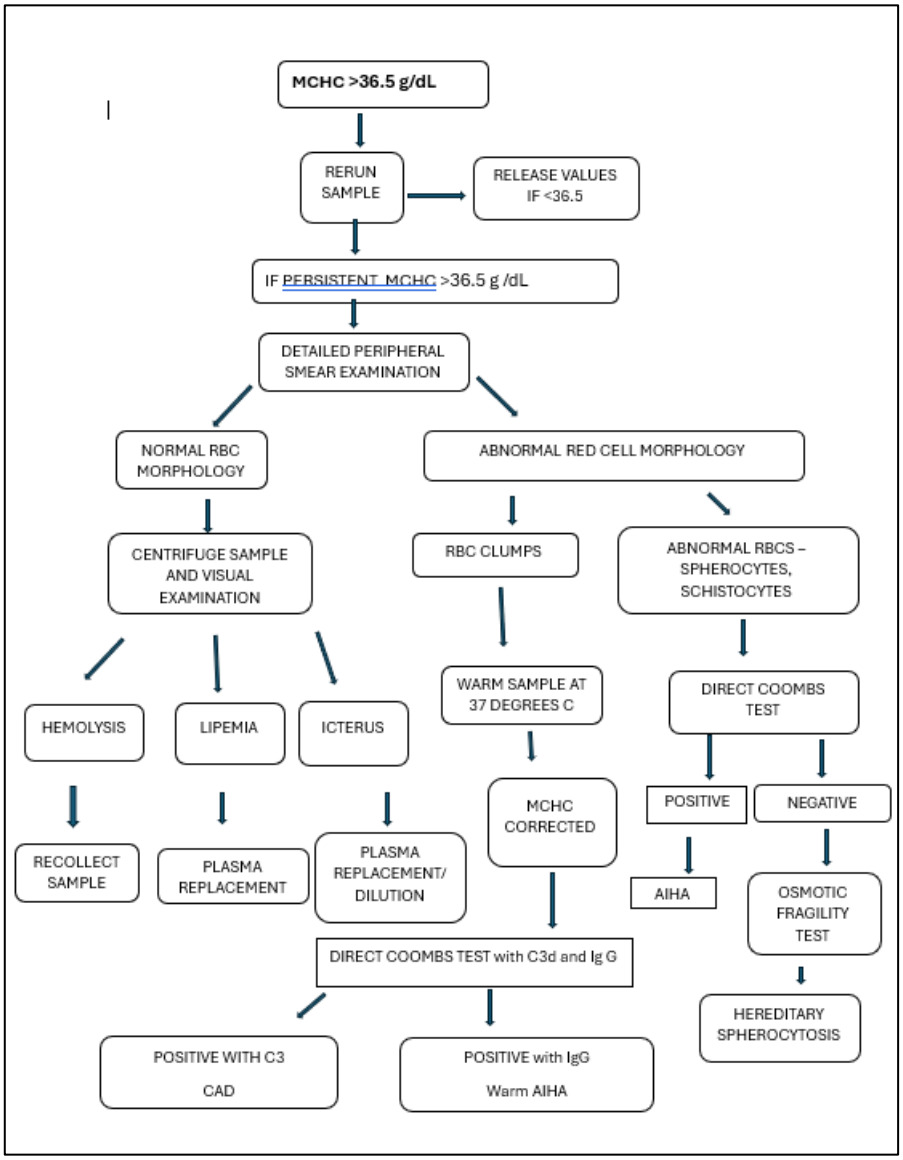

Figure 2: Summary of investigations and laboratory workup in case of elevated MCHC >36.5 g/dl or >365 g/l.[27]

Icterus

Icterus is one of the endogenous factors causing interference in clinical laboratory testing.[24] The visual observation of plasma is helpful in identifying interferences like icterus.[25] In some cases of hyperbilirubinemia (especially with bilirubin concentrations of 25–35 mg/ dl (425–600 µmol/l) there may be flag of 'Hb Interf' and falsely elevated Hb, MCH and MCHC may be seen. Clinical conditions associated with this finding are severe liver disease (hepatitis, cirrhosis), gallstones etc.

Visual examination of sample reveals yellow discoloration of serum or plasma in patients with icterus. Direct eye observation grading of icteric plasma is highly subjective and not standardized.[26] To obtain reliable results of blood indices, blood sample is diluted with an isotonic solution (preferably the diluent used in the analyzer), and sample is rerun. The results of WBC count, RBC count, Hb, Hct, and PLT count from the rerun should be appropriately corrected to account for the dilution. The MCV, MCH, MCHC, and RDW values can be reported as it is.

CONCLUSION

Elevated MCHC on automated hematology analyzers is an important finding and needs proper investigation and workup to reach a diagnosis and provide appropriate clinical care to the patients. However, this workup process might be time consuming and cause delay in patients reports. This article summarizes the various causes of

elevated MCHC and appropriate follow up investigations and corrective actions. Newer advanced hematology automated analyzers use CBC-O algorithm which reflexly initiates RET (reticulocyte) channel measurement and these reticulocyte parameters can in turn help to identify the causes of abnormal MCHC values like cold agglutinins, lipemia or hemolysis. As a result, the need for manual corrective procedures for MCHC correction is eliminated, thus significantly improving the turnaround time for CBC results. This will prove beneficial for optimal hematology reports and improved patient care.

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