National Policy and Procedure of Limitations and Corrective Actions for Automated Hematology Cell Counter Analyzer

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Acronyms:

AMR	Analytical Measurement Range
AIHA	Autoimmune Hemolytic Anemia
CBC	Complete Blood Count
CV	Coefficient of Variation
EDTA	Ethylenediaminetetraacetic Acid (anticoagulant used in hematology)
Hb	Hemoglobin
Hct	Hematocrit
HS	Hereditary Spherocytosis
IDA	Iron Deficiency Anemia
IgM	Immunoglobulin M
ISO	International Organization for Standardization
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MPV	Mean Platelet Volume
Na^+	Sodium Ion
NRBC	Nucleated Red Blood Cell
PLT	Platelet Count
QC	Quality Control
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
SLS-Hb	Sodium Lauryl Sulfate Hemoglobin (cyanide-free Hb method)
SOP	Standard Operating Procedure
WBC	White Blood Cell
µL	Microliter
g/dL	Grams per Deciliter
°C	Degrees Celsius
%CV	Percent Coefficient of Variation

HIL	Hemolysis–Icterus–Lipemia (interference index in some analyzers)
SIADH	Syndrome of Inappropriate Antidiuretic Hormone
BUN	Blood Urea Nitrogen
HPLC	High-Performance Liquid Chromatography
ESR	Erythrocyte Sedimentation Rate
CAP	College of American Pathologists
IQC	Internal Quality Control
EQA	External Quality Assessment
CV%	Coefficient of Variation (percentage)
HIL Index	Hemolysis, Icterus, Lipemia index (automated sample interference indicator)
HbA1c	Glycated Hemoglobin
Na^+/K^+	Sodium / Potassium ions

1. Purpose

To describe the limitations and analytical interferences encountered in automated haematology cell counters and to outline standardized corrective actions to ensure accuracy, precision, and reliability of patient results.

2. Scope

This procedure applies to all hematology staff performing Complete Blood Count (CBC) and related parameters using automated cell counter analyzers on EDTA-anticoagulated whole blood samples.

3. Definitions

3.1 Analyzer (Hematology Cell Counter): An automated instrument that measures and differentiates blood cells using electrical impedance and/or optical light scatter technology to generate a Complete Blood Count (CBC).

3.2 Interference: Any factor (pre-analytical, analytical, or patient-related) that causes a deviation of a laboratory result from the true value.

3.3 **Pre-Analytical Factors**: Conditions or processes occurring before sample analysis (e.g., collection, transport, storage) that can affect test accuracy.

3.4 **Analytical Factors**: Conditions or instrument-related issues occurring during analysis that affect measurement accuracy.

3.5 **Pathological / Patient Factors**: Biological or disease-related conditions in the patient's blood that interfere with analyzer measurements (e.g., cold agglutinins, lipemia, abnormal plasma viscosity).

3.6 **Lipemic Sample**: A sample containing high levels of lipids (triglycerides) causing plasma turbidity and optical interference, particularly with Hb measurement.

3.7 **Icteric Sample**: A sample with elevated bilirubin concentration leading to yellow discoloration of plasma and possible photometric interference in Hb assays.

3.8 **Hemolyzed Sample**: A sample in which red blood cells have ruptured, releasing free hemoglobin, potentially causing falsely low RBC and Hct readings.

3.9 **Cold Agglutinin**: Autoantibody that binds to red blood cells at low temperatures, causing RBC clumping and spuriously low RBC counts.

3.10 **Gray Platelets (Hypogranulated Platelets)**: Platelets appearing pale or agranular due to loss of granules, often caused by cold exposure or congenital Gray Platelet Syndrome.

3.11 **Cold Blood Sample**: A sample received at low temperature (<20 °C) causing temperature-dependent agglutination or altered platelet reactivity.

3.12 **Warm/Fresh Sample**: A newly collected specimen or one kept warm prior to analysis, which may show transient instability in indices before full anticoagulant mixing.

3.13 **Target Cells**: Red cells with a central area of hemoglobin surrounded by a pale zone and a peripheral ring, often seen in liver disease or thalassemia; may resist lysis during WBC counting.

3.14 **RBCs Resistant to Lysis**: Erythrocytes with abnormal membrane rigidity (e.g., sickle cells, spherocytes, target cells) that fail to lyse completely in analyzer reagents, causing falsely high WBC readings.

3.15 **Platelet Clumps**: Aggregates of platelets typically caused by EDTA-dependent antibodies or improper mixing, leading to spuriously low platelet counts.

3.16 **Abnormal Plasma Viscosity**: Increased plasma thickness due to elevated proteins (e.g., paraproteins, fibrinogen) altering blood flow and light scatter during analysis.

3.17 **Cryoglobulins**: Proteins that precipitate at low temperature, potentially causing clumping and optical interference in analyzers.

3.18 **Cold Sample Interference**: Analytical error occurring when blood sample temperature falls below recommended range, causing cell aggregation or altered indices.

3.19 **Nucleated Red Blood Cells (NRBCs)**: Immature red blood cells containing nuclei; counted erroneously as WBCs by some analyzers if not corrected.

3.20 **Carry-Over Contamination**: Cross-contamination of a low-value sample by a preceding high-value sample within the analyzer flow path

3.21 **Aperture Blockage**: Partial or complete obstruction of the analyzer's aperture by debris or fibrin, resulting in inaccurate counts or histograms.

3.22 **MCHC (Mean Corpuscular Hemoglobin Concentration)**: The average concentration of hemoglobin in a given volume of packed red blood cells.

3.23 **MCV (Mean Corpuscular Volume)**: The average volume of individual red blood cells.

3.24 **AMR (Analytical Measurement Range)**: The range of analyte concentrations that the instrument can accurately measure without dilution or special handling.

3.25 **QC (Quality Control)**: Procedures used to verify that analyzer performance is within acceptable limits using control materials of known values.

3.26 **Manual Verification**: Reassessment of results using manual methods such as microscopic review or manual counts when analyzer data are flagged or inconsistent.

3.27 **Flag (Instrument Flag)**: Automated message or warning generated by the analyzer indicating potential abnormality, error, or interference in a result.

3.28 **Cyanmethemoglobin Method**: The reference colorimetric method for hemoglobin determination in which hemoglobin is oxidized and measured at 540 nm.

3.29 **SLS-Hb Method**: A cyanide-free colorimetric hemoglobin measurement using sodium lauryl sulfate to form a stable-colored compound.

3.30 **Reducing Agents**: Chemical substances (e.g., ascorbic acid, glutathione) that donate electrons, potentially reducing hemoglobin during colorimetric measurement and causing falsely low readings.

3.31 **Hydrodynamic Focusing**: The technique by which cells are aligned in a single-file stream through the analyzer aperture using sheath fluid, ensuring accurate counting.

3.32 **Optical Scatter**: The deflection of laser light as it passes through cells, used by analyzers to determine cell size, granularity, and complexity.

3.33 **Flow Cell**: The chamber within a hematology analyzer where cells pass through a sensing zone for measurement by impedance or optical detection.

3.34 **Corrective Action**: Steps taken by laboratory personnel to resolve errors, verify accuracy, or reprocess samples affected by interferences.

3.35 **EDTA (Ethylenediaminetetraacetic Acid)**: Anticoagulant that chelates calcium to prevent blood clotting in hematology samples.

3.36 **Underfilled Tube:** Sample tube containing insufficient blood volume relative to anticoagulant, leading to RBC shrinkage or clot formation.

3.37 **Overfilled Tube**: Sample tube containing excessive blood relative to anticoagulant, resulting in incomplete mixing and microclot formation.

3.38 **Microspherocytosis**: Presence of small, dense RBCs with increased MCHC and decreased MCV.

3.39 **Pseudothrombocytopenia**: Spuriously low platelet count due to platelet aggregation.

3.40 **Corrective Action Log**: Laboratory record documenting identified interferences and remedial measures.

4. Policy

4.1 The laboratory acknowledges that automated hematology analyzers have analytical limitations and are subject to interferences that may affect accuracy and reliability of results.

4.2 All abnormal results, instrument flags, and discrepancies shall be reviewed before reporting.

4.3 No CBC result shall be released if:

4.3.1 QC is out of range

4.3.2 Analyzer flag is unresolved

4.3.3 Critical discrepancy between Hb,Hct,RBC indices exist

4.3.4 Delta check failure without investigation

4.4 Known limitations including but not limited to lipemia, icterus, hemolysis, cryoglobulins, cold agglutinins, extreme leukocytosis, platelet clumping, nucleated RBCs, and abnormal cell morphology must be assessed and addressed according to established corrective actions.

4.5 When analytical interference is suspected, appropriate corrective actions (e.g., sample warming, plasma replacement, dilution, centrifugation, manual smear review, rerun, or recollection) shall be performed before result release.

4.6 Any result exceeding the Analytical Measurement Range (AMR) must be processed according to dilution or reflex testing protocols prior to reporting.

4.7 Manual peripheral blood smear review shall be performed whenever analyzer flags indicate abnormal cell populations or when results are inconsistent with clinical information.

4.8 Corrected or modified results must be clearly documented in the Laboratory Information System (LIS), including details of the corrective action taken.

4.9 In cases where reliable results cannot be obtained, the sample shall be rejected and recollection requested with documented justification.

4.10 All troubleshooting steps must be documented and periodically reviewed for quality improvement.

4.11 This policy shall comply with international standards including CLSI guidelines and manufacturer instructions.

5. Procedure

5.1 Clinical background:

Complete blood count (CBC) parameters generated by automated hematology analyzers are critical for the diagnosis, monitoring, and management of a wide range of clinical conditions, including anemia, infection, inflammation, hematologic disorders, and malignancies. Accurate cell counts and indices directly influence clinical decision-making such as transfusion requirements, treatment initiation, and disease monitoring. However, pre-analytical and analytical factors, abnormal cell populations, and sample-related interferences may compromise result validity. Therefore, laboratory personnel must recognize analyzer limitations and apply appropriate corrective actions to ensure reliable results and optimal patient care.

5.2 Principle

Automated hematology cell counter analyzers measure blood cell parameters using electrical impedance, optical light scatter, and/or flow cytometry techniques to generate complete blood count (CBC) results. While these systems provide rapid and precise measurements, analytical accuracy may be affected by sample-related factors, abnormal cellular morphology, and instrument limitations. This SOP is based on recognizing analyzer flags, reviewing abnormal results, and applying defined corrective actions, such as sample reprocessing, dilution, microscopic examination, or recollection to ensure result validity and support safe clinical reporting.

5.3 Interferences and corrective actions

Category	Interference / Source	Effect on Analyzer / Result & Corrective Action by Laboratory Technologist
Pre-Analytical Factors		
Lipemic sample	- Turbid plasma (can appear milky) leads to falsely	Three methods: - 1. Plasma replacement (recommended)

Category	Interference / Source	Effect on Analyzer / Result & Corrective Action by Laboratory Technologist
	high Hb, MCH and MCHC due to light scatter .	- Centrifuge and replace plasma with isotonic diluent. - Rerun Hb and report as "Corrected (Cr) for lipemia. 2. Hb Calculation from HCT: The laboratory must use a locally validated formula established through method validation studies 3. Measure hemoglobin using point of care analyzer which is unaffected by lipemia If not corrected or unresolved, request fasting sample
Clotted and hemolyzed sample	- Clotted sample lead to Cell loss which falsely decrease WBC, RBC and PLT; Elizabeth May Flag 'clot detected'. - Hemolytic sample lead to falsly low RBC and Hct	- Reject specimen. - Notify clinician and request recollection ensuring proper EDTA Mixing to prevent clotting. - Record in sample rejection log - No correction permitted
Delay in analysis (>6 h) at room temperature	- RBC swelling (increase MCV and reduce MCHC) - PLT degradation.	- Check collection time, if delayed, request recollection. - Store future samples at 2–8 °C (can be tested within 24hrs).
Improper / vigorous mixing	- Uneven cell distribution or hemolysis.	- Invert tube gently 8–10 times before analysis; avoid vortexing.

Category	Interference / Source	Effect on Analyzer / Result & Corrective Action by Laboratory Technologist
Insufficient sample	- Aspiration of air leads to inaccurate counts or aborted run.	- Verify volume ≥0.5 mL - If inadequate, reject and recollect. - Do not re run sample tube repeatedly
Under filled EDTA	- Lead to cell shrinkage	- Reject and recollect new sample with emphasize on proper volume
Cold blood sample received	- Low temperature lead to RBC and PLT agglutination - Can falsly increase MCV,MCHC and reduce RBC count and Hct - Analyzer may flag "RBC agglutination" or "PLT abnormal distribution."	- Allow sample to reach room temperature (20–25 °C) before analysis. - If sample temperature < 20 °C, warm to 37 °C for 15–30 min. - Mix gently and rerun immediately. - If unresolved, perform manual RBC and PLT counts; note "cold-induced agglutination."
Warm / fresh sample received	- Recently collected or pre-warmed sample can temporarily affect RBC indices or cell stability if analyzed before full EDTA mixing; some cell types (e.g., platelets) may swell slightly.	- Ensure sample is gently inverted (8–10) times immediately after collection and prior to analysis - Verify histogram and indices; rerun if unstable.
Analytical / Instrumental Factors		
Carry-over contamination	- High sample affects next low sample.	- Run rinse or blank after high-value samples; repeat low sample.
Aperture blockage / clogging	- Fibrin/debris obstructs flow lead to low counts, abnormal histograms.	- Perform back-flush or cleaning cycle; - Rerun QC and sample.

Category	Interference / Source	Effect on Analyzer / Result & Corrective Action by Laboratory Technologist
Reagent deterioration / contamination	- QC drift, inaccurate results.	- Replace expired reagents. - Recalibrate - Verify QC.
Temperature / barometric variation	- Alters impedance or optical reading.	- Maintain analyzer room at 18–26 °C.
Electrical noise / grounding fault	- Random errors or spikes	- Check stability /grounding - Contact biomedical engineer if persistent.
Patient / Pathological Factors		
High WBC count (>AMR)	- Extremely high WBC falsely lead to high Hb, Hct, MCV due to turbidity or coincidence loss	- Dilute sample per analyzer protocol - Rerun the dilution - Corrected WBC= analyzer WBC result X dilution factor - Verify differential manually.
Cold agglutinin	- RBC clumping lead to reduce Hct and RBC count and increase MCV, MCH and MCHC, due to cold antibodies. WBC falsly increase or decrease - Analyzer 'Flag RBC agglutination'	- Warm sample to 37 °C for 15–30 min - Mix gently and immediately rerun. - If persistent, perform manual RBC count. - Pre & Post warming smear review
Platelet clumps / pseudo-thrombocytopenia And PLT satellitism	- PLT aggregates leads falsely low PLT. May falsely increase WBC count(pseudo thrombocytopenia)	- Examine smear for clumps (Feather edge) - Recollect in citrate tube and rerun

Category	Interference / Source	Effect on Analyzer / Result & Corrective Action by Laboratory Technologist
	- Usually, EDTA related.	- Correct platelet count using factor 1.1 (accounting for dilution effect of sodium citrate). - Other option to vortex the specimen for 1-2 mint and run the sample
Hemolyzed sample	- Falsely reduce RBC/Hct and increased Hb (free Hb interference).	- Reject if severe; request recollection; - If mild, note 'slightly hemolyzed sample' - interpret cautiously.
Gray platelets (hypogranulated)	- Platelets appear pale or a granular due to cold-induced degranulation or congenital gray platelet syndrome lead to falsely low PLT count. Giant platelet may be counted as RBC. - Analyzer flag "PLT abnormal distribution."	- Review smear for gray or hypogranular platelets. - If cold-related, warm sample and rerun. - Perform Impedance PLT count or manual PLT estimate if discrepancy persists. - Add report comment: "Gray platelets (hypogranulated) observed manual PLT verified."
Icteric sample	- Bilirubin absorbs light at Hb wave length lead to falsely high Hb, MCH and MCHC. - Suspect if Hb appears disproportionately high compared to HCT	- Options for correction: - 1. Use analyzer optical correction if available. - 2. Dilute the sample and rerun analysis - 3. Alternatively, can use hemecue (point of care testing) as it is less affected by icteric sample - Comment: "Hb verified icteric interference corrected."

Category	Interference / Source	Effect on Analyzer / Result & Corrective Action by Laboratory Technologist
Giant platelets	- Counted as WBCs leads to falsely decrease PLT count and increase WBC count. - It can rarely counted as RBC leading to high RBC count	- Confirm on smear; perform optical or manual PLT count - Document correction.
Microcytosis (IDA / thalassemia)	- Small RBCs counted as PLTs (especially in analyzers utilizing impedance technology leads to falsely high PLT count and high MPV	- Review MCV and smear - Use alternate method like optical technology if available to estimate the platelet count - Interpret result with morphology.
Microspherocytosis	- Small dense RBCs → ↓MCV, ↑MCHC; analyzer may flag "High MCHC."	- Review smear; correlate with history (HS, AIHA); - Report morphology comment: "Spherocytes present MCHC elevation due to morphology."
Resistance RBCs to lysis (e.g. target cells, rigid membranes, sickle cells)	- RBCs fail to lyse in WBC reagent leads to counted as WBCs; causes falsely high WBC, abnormal scatter & histogram peaks (extra peak between RBC and WBC zones).	Review analyzer flags and histograms. Examine blood smear for target or sickled cells. - Perform manual external lysing process; & Rerun - if abnormal pattern persists; preform manual WBC count & Blood smear Add report comment: "Possible interference by unlysed RBCs

Category	Interference / Source	Effect on Analyzer / Result & Corrective Action by Laboratory Technologist
Nucleated RBCs	- Counted as WBCs. - Many seen with neonatal samples	- Check if your analyzer is capable of reporting WBC count that has automatically been corrected for the presence of NRBCs, if not: - Apply correction: WBC (corrected) = WBC (reported) × [100 / (100 + NRBC %)]; document.
Red-cell fragments (schistocytes)	- Counted as PLTs.	- Confirm by histogram or scatter plot - Use optical/manual PLT count. - Perform blood smear
Cryoglobulins	- Cryoglobulins precipitation lead to high WBC and PLT estimation as well high Hb, MCHC and low RBC count	- Warm to 37 °C if cryoglobulin suspected for 15-30 min and rerun. - Pre & Post warming smear review - Can do plasma replacement using a warm isotonic diluent maintained at 37C.
Paraproteins	- Protein precipitation due to paraproteinemia leads to falsely low RBC count, high Hb, MCH and MCHC.	- Do plasma replacement using a warm isotonic diluent - Correlate with serum protein electrophoresis - Inspect plasma; verify counts manually if abnormal. - Examine the blood film for confirmation of rouleaux formation
Extreme dehydration / overhydration	- Alters RBC indices, Hb and Hct.	- Correlate with clinical chemistry and patient status. (Serum Na^+, BUN,

Category	Interference / Source	Effect on Analyzer / Result & Corrective Action by Laboratory Technologist
		Creatinine, Total Protein, and Albumin)
Microorganisms	- Bacteria, fungal(yeast) and malarial parasite in high concentrations can cause falsely high PLT and /or WBC counts	- Check histograms, scattergrams - Correct count manually by blood film - Correlate with blood culture report - Repeat sample if contamination is suspected
Dilution with IV fluid infusion	- Diluted the sample which leads to low WBC, RBC, Hb, Hct and PLT counts	- Check previous results - Compare with chemistry results - Request new sample, collected properly

5.4 Quality Control

- Run three levels of commercial control (low, normal, high) daily.
- Monitor Levy-Jennings charts and investigate out-of-range results.
- Record all corrective actions in the QC and analyzer maintenance logs.
- Perform preventive maintenance and cleaning per manufacturer's instructions.

5.5 Documentation and Reporting

- Record every interference and corrective action in the **Hematology Interference/Corrective-Action Log**.
- Include interpretive comments in patient reports (e.g., *"Result corrected for lipemia interference."*).
- Inform the pathologist or supervisor of unresolved analytical anomalies.
- Retain all documentation per institutional record-keeping policy.

5.6 Safety Considerations

- Treat all blood specimens as potentially infectious.
- Follow universal precautions; wear gloves, lab coat, and protective eyewear.
- Dispose of biological waste according to biosafety and local regulations.

6. Responsibilities

6.1 Laboratory Technologists / Scientists:

- Detect, troubleshoot, and record analytical interferences; apply appropriate corrective actions before result release.
- Staff must demonstrate documented annual competency in analyzer troubleshooting and interference management

6.2 Chief MLS Officer / Supervisor:

- Ensure implementation of this SOP, staff competency, and review of QC and corrective-action logs.

6.3 Laboratory Director / Pathologist:

- Review unresolved or critical analytical discrepancies and authorize result interpretation.

7. Document History and Version Control

Version	Description	Review Date
1	Initial Release	August 2031

8. References

1. CLSI H20-A2: *Reference Leukocyte (WBC) Differential Count and Evaluation of Instrumental Methods.*
2. WHO *Laboratory Manual for Haematology*, 2021 Edition.
3. Manufacturer's Analyzer Operator Manual (Sysmex, Beckman Coulter, Mindray, Horiba, Abbott etc.).

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