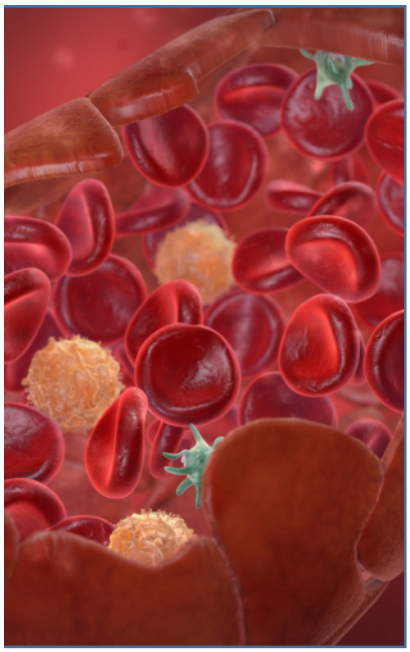
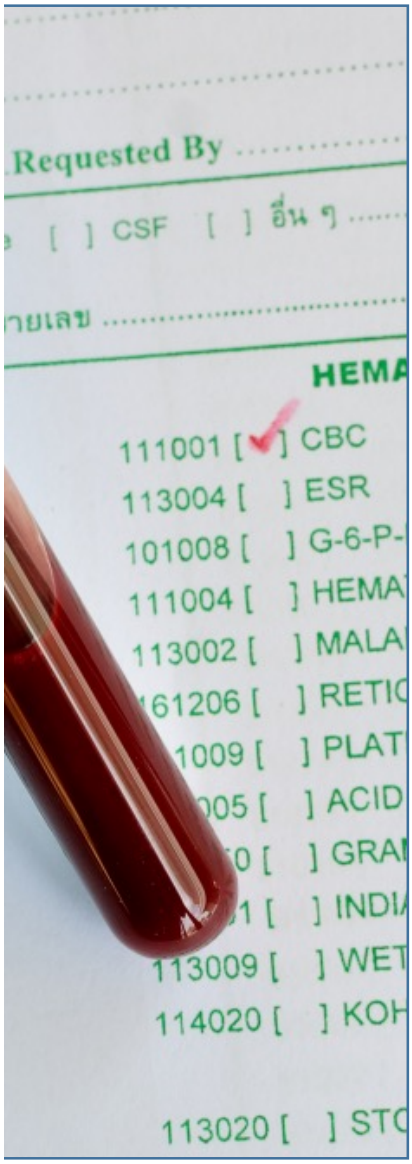
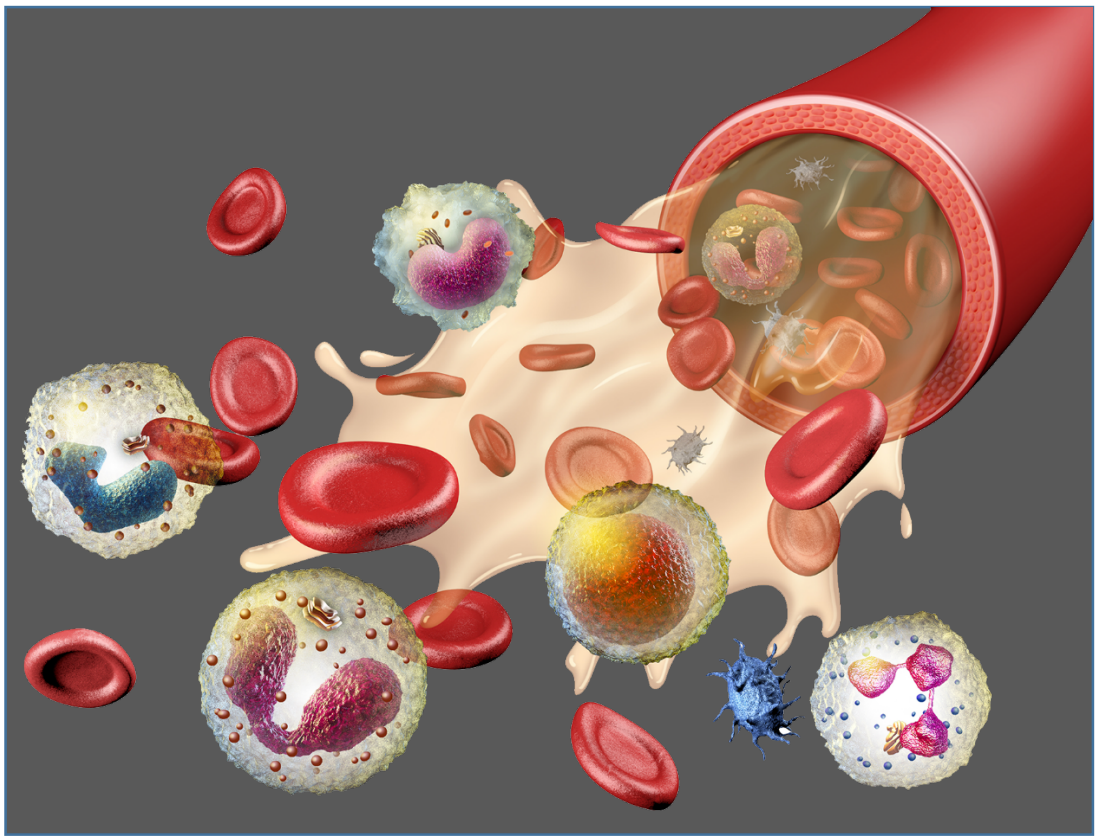


New Blood Cell Counting Technology in the VCUHS Hematology Laboratory

Hematology Laboratory Faculty and Staff

March, 2017





On March 7, 2017, the VCUHS Clinical Laboratories will introduce a new, top-of-the line automated CBC analyzer (i.e., hematology analyzer) track line (Sysmex XN-9000) in the main Hematology Laboratory. Similar Sysmex technology will also be used in the other VCUHS laboratories providing cellular analysis, including the Emergency Department Laboratory, Stony Point Laboratory, Children's Hospital Laboratory, and Transplantation Laboratory. This change was instituted because recent technological developments in cellular analysis and computer software have led to improved analytic efficiency and new cellular analytic parameters of clinical significance. In addition to the conventional CBC parameters and five-part leukocyte differential count, the new hematology analyzers provide an extended leukocyte differential, with quantitative information regarding cells that do not normally occur in the peripheral blood, such as blasts, immature granulocytes, atypical leukocytes, and nucleated red blood cells (NRBCs). In addition, they provide additional information about reticulocytes and platelets that is of great value in patient diagnosis and management.

Sysmex Technology

The Sysmex automated CBC analyzers use the following technologies to measure and count circulating blood cells and cellular components: (1) direct current impedance, (2) advanced optical light scatter technology, (3) fluorescent flow cytometry, and (4) spectrophotometry.

The WBC, RBC, platelet counts, hemoglobin, and hematocrit are measured directly in the Sysmex instruments using a WBC channel, a RBC/platelet channel, and a separate hemoglobin channel. WBC and RBC counts are obtained using impedance technology, which is enhanced by a sheathed stream with hydrodynamic focusing in the RBC/platelet channel, and by floating thresholds in the WBC/platelet channel to accurately discriminate cell populations. Although other CBC analyzers use the conventional modified cyanohemoglobin technique to measure hemoglobin concentration, the Sysmex instruments utilize a sodium lauryl sulfate (SLS) reagent, which forms a stable complex with oxidized hemoglobin, and is measured photometrically at 555 nm to minimize interference by turbidity and other interferences.

Various cellular indices are calculated from the direct measurements by the CBC analyzer, including the MCV, MCH, MCHC, RDW-SD, RDW-CV, MPV, and plateletcrit. The RDW-CV is the conventional RDW reported as a CV. The RDW-SD is a new parameter representing the RBC arithmetic distribution width measured at 20% of the height of the RBC curve, reported in femtoliters (fL), with a reference interval of 37 to 54 fL. The plateletcrit is the platelet volume ratio, analogous to the hematocrit. MPV is calculated from the plateletcrit and platelet count in the same manner as the erythrocyte MCV.

Fluorescent flow cytometry using a polymethine dye is used to determine the WBC, WBC differential, and the enumeration of nucleated RBCs. In the Sysmex XN-9000, the three separate channels are used for these measurements. The white cell nucleated (WNR) channel is used for WBC, NRBC, and basophil counting, while neutrophils, lymphocytes, monocytes, eosinophils, and immature granulocytes are determined from the WBC differential (WDF) channel. If blasts or abnormal lymphocytes are detected by the instrument, subsequent analysis is performed in a special white precursor cell (WPC) channel. The WBC count is automatically corrected when NRBCs are detected in the sample.

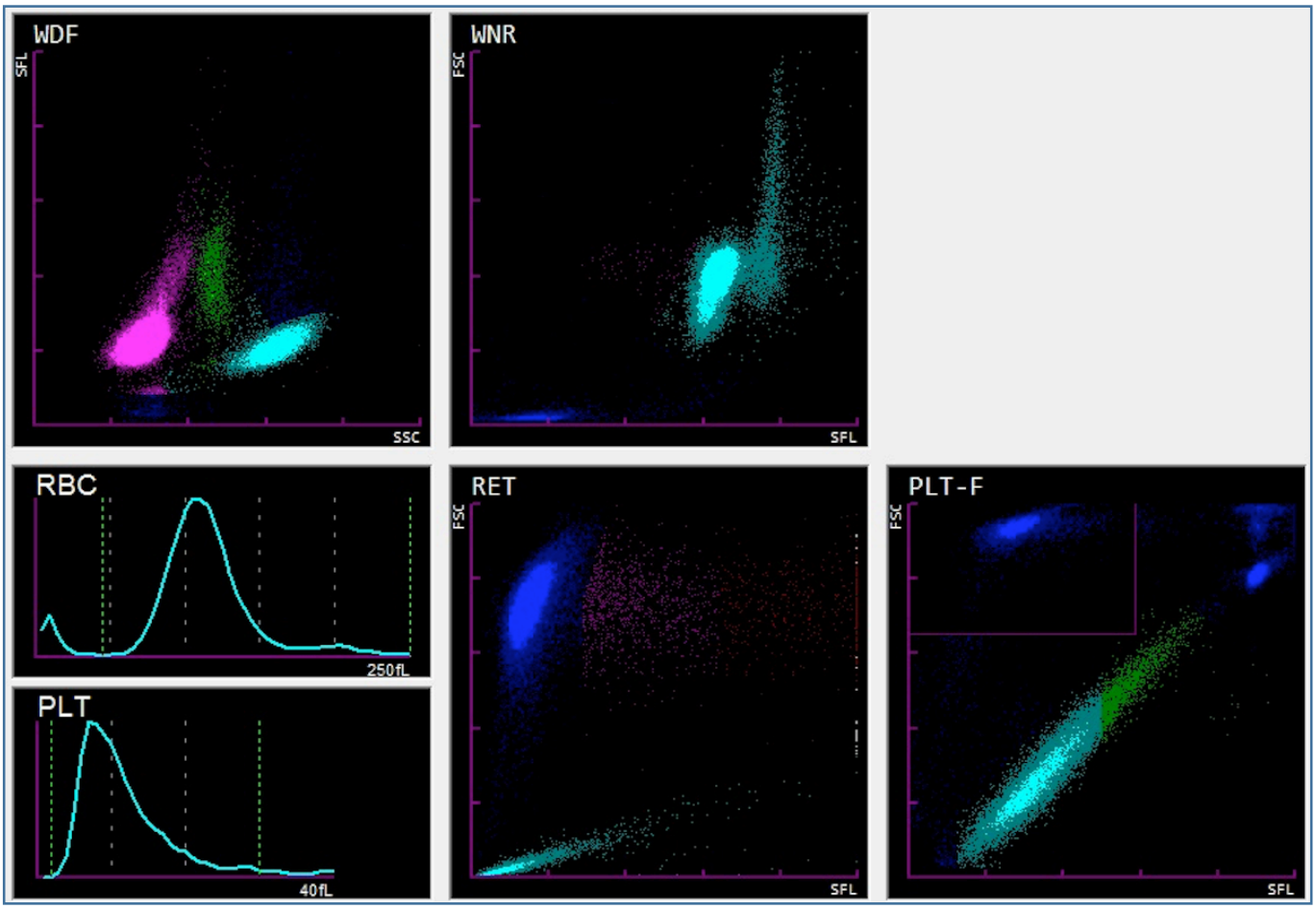


Fig. 1. Sysmex XN-9000 histograms from a patient with chronic lymphocytic leukemia (CLL). In the WDF channel (upper left) the lymphocyte population is pink, monocytes are bright green, and neutrophils are aqua. In the WNR channel (upper middle) debris is dark blue and leukocytes are aqua. RBC and PLT histograms are shown (lower left). In the RET channel, the red blood cell population is purple, and reticulocytes are pink. Mature platelets are aqua in the PLT-F channel, while the immature PLT fraction is bright green.

In addition to conventional impedance and optical methods for counting platelets, a novel fluorescent PLT (PLT-F) channel uses a fluorescent RNA dye (oxazine) in combination with extended PLT counting volume and time for platelet counting and determination of the immature platelet fraction (IPF).

Specimen Requirements, Processing, and Laboratory Analysis

The routine specimen requirement for the CBC and CBC with differential for Sysmex analysis is a 3 mL lavender top (K_2EDTA) tube. 500 uL capillary blood collection (Microtainer) tubes will be accepted for pediatric patients. The analysis will be available on all shifts and days of the week (24/7/365). Specimens should be delivered within four hours of collection. However, remote locations can be refrigerated at 20-8^{o}C for up to 24 hours if testing cannot be completed within 4 hours of collection. Under these circumstances, transportation to the laboratory should be in a transport cooler containing cold packs.

Table 1
Adult Blood Cell Reference Ranges

Parameter	Female	Male	Units
WBC	3.9 - 11.7	3.7 - 9.7	x 10^9 cells/L
RBC	3.85 - 5.16	4.54 – 5.78	x 10^{12} cells/L
HGB	12.0 - 15.0	13.3 - 17.2	g/dL
HCT	34.8 - 45.0	38.9 - 50.9	%
MCV	78.5 - 96.4	81.2 - 94.0	fL
MCH	25.6 – 32.2	25.7 – 32.2	pg
MCHC	30.5 – 34.0	30.9 – 35.5	g/dL
RDW-CV	11.3 - 14.7	11.5 - 14.1	%
RDW-SD	36.4 – 46.3	35.1 – 43.9	fL
PLT	172 - 440	179 - 373	x 10^9 cells/L
MPV	8.7 – 12.3	8.7 – 12.1	fL
IPF	0.0 – 9.9	0.0 – 9.9	%
NEU#	1.9 - 7.9	2.0-6.7	x 10^9 cells/L
LYM#	1.3 - 3.6	1.1 - 3.3	x 10^9 cells/L
MONO#	0.3 – 0.7	0.2 – 0.7	x 10^9 cells/L
EOS#	0.0 – 0.4	0 – 0.4	x 10^9 cells/L
BASO#	0.0 – 0.1	0 – 0.1	x 10^9 cells/L
nRBC%	0.0 – 0.20	0.0 – 0.20	% (/100WBC)
% Retic	0.9 – 2.6	0.8 – 2.5	%
Absolute Retic Count	0.0377 – 0.1222	0.0436 – 0.1305	x 10^6 cells/L
IRF	2.3 – 13.4	2.3 – 13.4	%
RET-He	32.1 – 39.1	32.1 – 39.1	pg

Continuous orders will need to be re-ordered in Cerner to continue to be performed by the new method.

Turnaround time for results is 1 hour for Stat specimens and 4 hours for routine analysis. Adult reference ranges for Sysmex blood cell counts and indices is given in the following table, and will be included with the patient result. Pediatric reference ranges will be provided with the patient report and are available on the pathology department web site at the following address (http://www.pathology.vcu.edu/clinical-services/clinical-pathology/hematology).

The Sysmex instruments are very sensitive to the presence of abnormal blood cells and blood cell counts generate “flags” to alert the cell counter operator to the presence of specimen abnormalities. If a significant abnormality is identified, a blood film is automatically prepared for further review by a technologist using digital cell morphology (Cellavision) technology and possibly a light microscope. The results may be released to the Cerner chart by the technologist, but may be referred to an attending hematopathologist for consultation if certain criteria are met. If the results are medically significant or exceed a critical value, the ordering physician will be notified by telephone and a comment entered in the Cerner result.

New FDA-Approved Reportable Cellular Parameters

The complete blood count (CBC) with differential performed in the main VCUHS Hospital Hematology Laboratory. will now include cell counts (RBC, WBC, and PLT), a five part differential count, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW-CV,

reticulocyte % reticulocytes, absolute reticulocyte number, Immature Reticulocyte Fraction (IRF), Reticulocyte Hemoglobin (RET-He), Nucleated Red Blood Cell (nRBC) Count, and Immature Platelet Fraction (IPF). The IPF will not be available from specimens analyzed in the Transplantation Laboratory. The new tests are an extension of the traditional CBC and require no additional blood sample. The Immature Granulocyte (IG) count is under review by the laboratory and will be available at a later time, with notification from the laboratory.

Reticulocyte Hemoglobin (RET-He) and Immature Reticulocyte Fraction (IRF): Reticulocyte counts are the quantity of the youngest erythrocytes normally released from the bone marrow into circulating blood. Automated analysis has led rapid and very accurate reticulocyte counting, as well as providing the reticulocyte immature reticulocyte fraction (IRF), the reticulocyte hemoglobin content (RET-He), and other parameters. The IRF assesses reticulocyte maturation by measuring the intensity of mRNA staining, with the youngest reticulocytes having the highest content. IRF has been proposed as an early marker of engraftment in bone marrow or hematopoietic stem cell transplantation and bone marrow regeneration following chemotherapy. RET-He is a reliable marker of cellular hemoglobin content that is useful in assessing the functional iron available for erythropoiesis during the previous 3–4 days. Published data show a RET-He cut-off of 29 pg/cell as an indication of iron deficiency. A value below this range is indicative of a decreased amount of iron incorporation into the RBC or iron deficiency. There is a good agreement between the RET-He and the CHr measured by other automated cell counters. These indices correlate with iron-deficient erythropoiesis and are useful markers of iron deficiency in infants and children, adult blood donors, geriatric patients, pregnant women, and patients with chronic kidney disease undergoing hemodialysis. In addition, the RET-He is a useful in monitoring the response to iron replacement therapy and detecting iron-restricted erythropoiesis in patients receiving erythropoietin therapy. There is also intense interest in using these parameters to evaluate and monitor patients with complex anemia associated with malignancy.

Nucleated Red Blood Cells (NRBC): Nucleated red blood cells are immature erythrocytes that are commonly found in the circulation during pregnancy and the very early neonatal period. However, the finding of nRBCs at other times usually indicates markedly increased erythroid activity, or

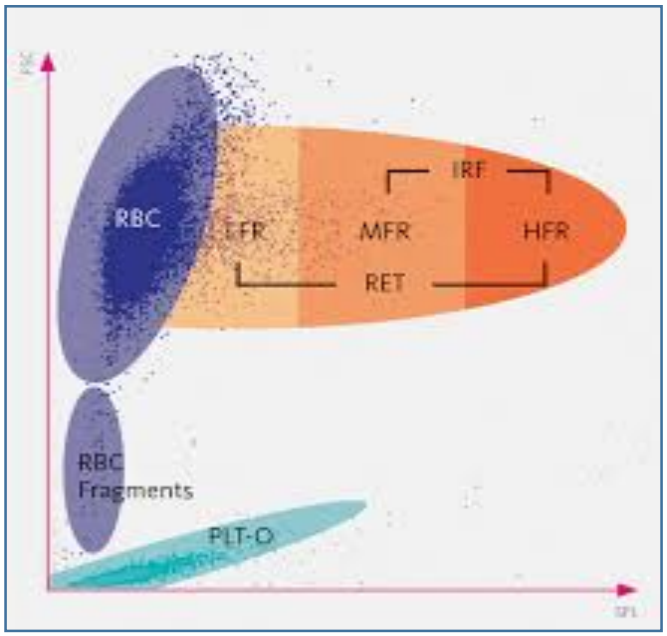


Fig. 2. Histogram of RET channel showing location of reticulocytes in comparison to mature RBCs (blue). The three stages of reticulocyte maturation include low fluorescence reticulocytes (LFR), medium fluorescent reticulocytes (MFR), and high fluorescent reticulocytes (HFR). The combination of the two most immature stages of maturation, MFR and HFR, comprise the immature reticulocyte fraction (IRF).

Table II
Summary of Sysmex Parameters

Sysmex Parameters FDA-Approved and Reported at VCUHS		
Parameter	**Technology**	**Units reported**
Red blood cell count	Impedance with hydrodynamic focusing	RBC (x 10^{12} cells/L)
Hemoblobin	RBC lysis by SLS, photometry at 555 nm	Hgb (g/L)
RBC indices	Impedance, calculations, and histogram analysis	Hematocrit, MCV, MCH, MCHC, RDW-CV
Reticulocyte count	Fluorescent flow cytometry	% and absolute count
Immature reticulocyte fraction	Fluorescent flow cytometry	IFR (%)
Reticulocyte hemoglobin	Fluorescent flow cytometry	RET-He (pg)
Nucleated red cell	Fluorescent flow cytometry	nRBC (%/100 WBC)
White blood cell count	Fluorescent flow cytometry	WBC (x 10^{9} cells/L)
WBC Five-Part Differential	Light scatter and fluorescent flow cytometry	NEU#, NEU%, LYM#, LYM%, MONO#, MONO%, EOS#, EOS%, BASO#, BASO%
Platelet count	Impedance and fluorescent flow cytometry	PLT (x 10^{9} cells/L)
Parameter	Technology	Units reported
Red blood cell count	Impedance with hydrodynamic focusing	RBC (x 10^{12} cells/L)
Hemoblobin	RBC lysis by SLS, photometry at 555 nm	Hgb (g/L)
Sysmex Parameters Non-FDA Approved and/or Not Reported at VCUHS		
RDW-SD	Calculation	RDW-SD %
Immature granulocyte fraction	Fluorescent flow cytometry	IG (%)
Neutrophil granulation (NEUT-SSC)	Light scatter and fluorescent flow cytometry	NEUT-SSC
Fragmented red cells (FRC)	Fluorescent flow cytometry	FRC (# and %)
Microcytic and Macrocytic Red Blood Cell Populations	Histogram analysis	MicroR and MacroR (%)
Hypo-Hemoglobinized and Hyper-Hemoglobinized Red Blood Cells	Fluorescent flow cytometry	HYPO-He and HYPER-H*e* (%)

damage to the bone marrow microenvironment from a hematologic neoplasm or metastatic malignancy. In these conditions, the presence of circulating nRBCs is a poor prognostic indicator. Until recently, it was virtually impossible for hematology analyzers to distinguish small mature lymphocytes from nRBCs. At that time, the only reliable method for enumerating circulating nRBCs was manual counting of peripheral blood smears, usually using a 100 cell count, with significant intra- and interobserver reproducibility and sampling error. Earlier automated nRBC enumeration by different hematology analyzers was also limited by low sensitivity and specificity, especially when dealing with low numbers of nRBCs. In contrast, the Sysmex hematology analyzers use advanced light scattering techniques and fluorescence to rapidly and accurately detect NRBCs even at clinically significant low numbers.

Immature Platelet Fraction (IPF): Circulating immature platelets are much larger platelets that have been recently released from the bone marrow. IPF have a greater

RNA content, and can be measured by automated hematology analyzers, including the Sysmex instruments in the same manner as immature reticulocytes, and they are reported as percentage of the total platelet count (% IPF). It is well accepted that a high IPF is usually found in either consumptive or recovering thrombocytopenic disorders, while a low IPF is characteristic of bone marrow suppression disorders. Thus, the IPF is an index of thrombopoiesis and it may assist the physician in determining the cause and differential diagnosis of thrombocytopenia when used with patient information and the platelet count. IPF may help the physician determine if thrombocytopenia is due to platelet destruction or decreased platelet production. In addition, many studies have also shown that the IPF is an early indicator of marrow recovery in patients rebounding from chemotherapy or hematopoietic stem cell transplant. IPF recovery, denoted as levels >7.0%, occur on average 3.1 days earlier than platelet count recovery, and 3.8 days earlier than absolute neutrophil count recovery. Thus, the IPF may be useful to guide and possibly limit prophylactic platelet transfusions in patients undergoing marrow suppressive therapy, in view of imminent recovery of the platelet count.

Immature Granulocyte count (IG): Historically, measurement of the proportion of the circulating neutrophil population that are bands (i.e., band count) has been considered clinically useful for the diagnosis of infection, especially for neonatal sepsis. Since automated hematology analyzers could not accurately differentiate bands from neutrophilic granulocytes at other stages of maturation, manual counting using a light microscope was used for band counts. However, multi-institutional studies conducted by the College of American Pathologists and other organizations showed that band counts were inaccurate and imprecise due to the inability of technologist to reproducibly identify band neutrophils. During the past decade, most hospitals have stopped performing manual band counts for this reason. Fortunately, other immature granulocytes (IGs) including metamyelocytes, myelocytes, and promyelocytes have better morphological definition and together can be used as an alternative to the band count. In addition, IGs are usually not detected in healthy individuals but are elevated in patients with bacterial infections, acute inflammatory disorders, cancer (marrow metastasis), tissue necrosis, acute transplant rejection, surgical and orthopedic trauma, myeloproliferative neoplasm, steroid use, and pregnancy. An increase in IGs is usually accompanied by an increase in the absolute neutrophil count (ANC), but elderly patients, neonates, and patients with myelosuppression may have elevated IGs without an elevation of the ANC. Sysmex XN hematology analyzers perform the IG count as a part of the leukocyte differential count with notably low imprecision (CV near 7%). In addition, the accuracy of these measurements compared to microscopic examination or flow cytometry with monoclonal antibodies has been shown to be high. The ability to provide a more accurate and precise automated immature granulocyte count without performing a manual differential will decrease turnaround times to provide patient results sooner. The VCUHS Hematology Laboratory is presently evaluating this parameter in our hospital.

New Non-FDA-Approved, Non-Reportable Cellular Parameters

A number of measurements and calculations are performed during automated cell analysis that have not been FDA-approved, will not be reported with the patient results,

and cannot be used for *in vitro* diagnosis. These parameters should be considered experimental, and include measurements of neutrophil granularity (NEUT-SSC), fragmented red blood cells (FRC*), hypochromic red cells (%HYPO-He), hyperchromatic red cells (%HYPER-He), macrocytic red cells (MacroR), and microcytic red cells (MicroR). With appropriate IRB-approval and collaboration with the hematology laboratory faculty, these parameters can be made available for research studies in patients with anemia and other diseases. In addition, research investigations involving the RDW-SD, immature granulocyte count, immature platelet count, RET-He and other analytic parameters are greatly needed to expand knowledge in this area. The hematopathology faculty is most willing to collaborate with the faculty and housestaff of other departments with a research interest in blood cell counts and parameters.

Neutrophil Granulation (NEUT-SSC): Light scattered at a 90^{o} angle from the axis of a laser beam (side scatter, SSC) is altered by the internal complexity of cells passing through the laser beam and analysis of SSC provides information about the cytoplasmic density and number of cytoplasmic granules in a cell population. Among the peripheral blood leukocyte population, neutrophils and eosinophils exhibit the highest SSC, in comparison the monocytes and lymphocytes. The Sysmex cell counters analyze the side-scattered light (SSC) of the WDF channel to generate the parameter NEUT-SSC, which is a measure of the granularity of the neutrophil population. A low NEUT-SSC value indicates a hypogranular neutrophil population, while the NEUT-SSC value is increased in hypergranularity. Neutrophil hypogranularity is a common feature of neutrophil dysplasia found in the myelodysplastic syndromes (MDS) and some myeloproliferative disorders such as chronic myelomonocytic leukemia (CMML) and atypical chronic myeloid leukaemia (aCML). Neutrophil hypergranularity is exhibited in the reactive neutrophils found in patients with an infection or acute phase reaction. The automated detection of hypogranular neutrophils is potentially of great diagnostic value in differentiating between MDS and reactive and benign idiopathic and hereditary causes of neutrophilia, especially when used in conjunction with absolute cell counts, the immature granulocyte count, and other parameters.

Fragmented Red Blood Cells (FRC*): The Sysmex cell counters analyze a specific area of the reticulocyte (RET) histogram to determine the number and percentage of fragmented red blood cells (FRC% and FRC#). Fragmented red blood cells are usually a consequence of mechanical damage induced by turbulent blood flow or contact of the red cells with a pathologically altered endothelium. These abnormal shear forces damage the red blood cells, producing cell remnants that appear as ‘helmet’ cells, schistocytes and other odd shapes that are collectively termed “fragmented red cells” when viewed under a microscope. The finding of fragmented red cells by manual light microscopy has been used for decades to differentiate disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia purpura, and similar diseases from other causes of hemolytic anemia. The subjective automated measurement of this parameter should greatly increase the diagnostic efficacy of hemolytic anemia diagnosis. Forthcoming advanced red cell morphology analytic software for the Cellavision digital morphology analyzer should complement the Sysmex FRC parameter.

Microcytic and Macrocytic Red Blood Cell Populations: Measurement of the proportion of the red blood cell population that is microcytic and macrocytic is determined in the Sysmex cell analyzers by analysis of the RBC size distribution (i.e., MCV) histogram produced by the RBC/PLT channel. In this channel, hydrodynamic focusing with sheath flow direct current) impedance is used to count RBCs and platelets (PLT) and produce the histogram. Normally, this histogram shows a nearly Gaussian distribution, but may be skewed in patients with microcytosis of macrocytosis. The percentage of microcytic (MicroR) and macrocytic (MacroR) cells is determined by placing discriminators at the lower and upper area of the histogram. These parameters are helpful in refining the diagnosis of anemia, since the MCV can be normal, even in the presence of dimorphic red cell populations or increased microcytic or macrocytic red cells.

Hypo-Hemoglobinized (HYPO-He) and Hyper-Hemoglobinized (HYPER-He) Red Blood Cells: HYPO-He is the percentage of RBC with a cellular hemoglobin content lower than 17 pg, whereas HYPER-He is the percentage of RBC with a cellular hemoglobin content higher than 49 pg. There parameters are determined in the reticulocyte (RET) channel, where they are derived from a measurement of the hemoglobin content of all mature RBC (RBC-H_e). In conjunction with the reticulocyte count, IRF, RET-He and other parameters, the HYPO-He and HYPER-He are useful in predicting, diagnosing, and monitoring iron deficiency in patients with chronic renal failure and other diseases.

Other Parameters: The Sysmex XN-9000 analyzer is capable of providing an extended leukocyte differential count with as many as 22 parameters that are generated with the CBC. In addition to the parameters discussed above, these include neutrophil complexity and width of dispersion (NE-WX), neutrophil fluorescence intensity (NE-SFL), neutrophil fluorescence intensity and the width of dispersion (NE-WY), neutrophil cell size (NE-FSC), neutrophil cell size and the width of dispersion (NE-WZ), lymphocyte cell complexity (LY-X), lymphocyte complexity and width of dispersion (LY-WX), lymphocyte fluorescence intensity (LY-Y), lymphocyte fluorescence intensity and the width of dispersion (LY-WY), lymphocyte cell size (LY-Z), lymphocyte cell size and the width of dispersion (LY-WZ), monocyte cell complexity (MO-X), monocyte complexity and width of dispersion (MO-WX), monocyte fluorescence intensity (MO-Y), monocyte fluorescence intensity and the width of dispersion (MO-WY), monocyte cell size (MO-Z), and monocyte cell size and the width of dispersion (MO-WZ).

Additional information

Copies of this brochure are available on the VCUHS hematology laboratory web site (http://www.pathology.vcu.edu/clinical-services/clinical-pathology/hematology). Additional information can be obtained from Client Services at 804-828-PATH, or from the hematopathology faculty. A complete bibliography in EndNote format is available from Dr. Riley (roger.riley@vcuhealth.org). The following webinars are also available:

Measurement of immature cells in peripheral blood (https://www.youtube.com/watch?v=z7lGJqSLuAw)
Utility of RET-He (https://www.youtube.com/watch?v=93gYGZ7CWEY)
Utility of IPF (https://www.youtube.com/watch?v=zcBxQnDDtAc)
Utility of IG (https://www.youtube.com/watch?v=bBG1O-0zcao)
Case studies demonstrating the clinical application of the advanced clinical parameters (https://www.sysmex.com/us/en/Education/Webinars/Pages/LearnMore.aspx?WebinarID=67&Upcoming=0)

Acute anemia toolkit: bloodless strategies to optimize patient outcomes (https://www.sysmex.com/us/en/Education/Webinars/Pages/LearnMore.aspx?WebinarID=74&Upcoming=0)
A clinical overview and discussion of laboratory medicine in an oncology practice (http://www.sysmexamerica.com/CRC/Webinars/Pages/LearnMore.aspx?WebinarID=63&Upcoming=0)

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