EDUCATIONAL COMMENTARY – CLINICAL APPLICATIONS OF NEW PARAMETERS AVAILABLE FROM AUTOMATED HEMATOLOGY ANALYZERS

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Learning Outcomes

On completion of this exercise, the participant should be able to

• define new parameters available from automated hematology instruments that enhance the routine complete blood cell count;
• describe clinical applications for the new automated parameters;
• correlate results from new automated parameters with various patient conditions; and
• discuss how the new automated parameters can improve patient outcomes.

Introduction

Many enhancements in hematology instrumentation have been introduced since the first automated analyzers provided only white blood cell and red blood cell counts. Although “routine” tests are available from all hematology instruments, the automated hematology analyzers now available can provide clinicians with additional relevant data that can directly improve the quality of patient care. These newly developed tests have been called advanced clinical parameters and include the immature reticulocyte fraction, reticulocyte hemoglobin concentration, immature platelet fraction, immature granulocyte population, and red blood cell subpopulations.

Immature Reticulocyte Fraction

Absolute and relative reticulocyte counts have been available for several years as reportable results from automated analyzers. Two more recent advanced clinical parameters are the immature reticulocyte population or fraction, and the reticulocyte hemoglobin concentration or content.

The immature reticulocyte fraction represents reticulocytes with an increased level of ribonucleic acid (RNA). Determining the number of immature reticulocytes can be useful in assessing the erythropoietic activity of the bone marrow, which in turn provides diagnostic and therapeutic information. The immature reticulocyte fraction is usually expressed as the subpopulation of reticulocytes that demonstrates the most RNA, which are young reticulocytes most recently released from the bone marrow to the peripheral blood.

The immature reticulocyte fraction is useful as an indicator of bone marrow regeneration after engraftment or ablative treatment. Even before other early indicators such as reticulocyte, white blood cell, or platelet counts rise, an increase in the immature reticulocyte fraction indicates successful bone regeneration.
marrow recovery. Likewise, measuring the immature reticulocyte fraction has proven useful in monitoring response to erythropoietin therapy, as in patients with kidney transplants. In addition, some researchers suggest that the immature reticulocyte fraction could be a cost-effective substitute indicator, instead of CD34 enumeration, to indirectly measure stem cell response after treatment with growth factors.¹

The parameter may also be clinically useful in distinguishing among anemias, especially in differentiating those associated with increased bone marrow erythropoiesis, such as hemolytic anemias, from conditions linked to decreased marrow production, such as the anemia of chronic renal disease. In hemolytic anemias, the immature reticulocyte fraction will be increased. In bone marrow production problems, the value will be decreased. Furthermore, the immature reticulocyte fraction may be helpful in monitoring therapy in patients with megaloblastic and iron deficiency anemias. In these conditions, when treatment is effective, the immature reticulocyte fraction increases several days before an increase is seen in the total reticulocyte count. Some anemias, such as that seen in myelodysplastic syndromes, will present with a low normal reticulocyte count but an elevated immature reticulocyte fraction. The immature reticulocyte fraction can be helpful in distinguishing these various anemias.

Reticulocyte Hemoglobin Concentration

The reticulocyte hemoglobin concentration reported by automated hematology analyzers has become a useful tool in assessing the functional availability of iron for developing red blood cells and as an overall measure of erythropoiesis. These applications are especially helpful in the evaluation of iron status and in the management of iron or erythropoietin treatment.

The reticulocyte hemoglobin content reflects the ability of immature erythrocytes to incorporate iron into hemoglobin. This parameter indicates whether enough iron is available for erythropoiesis as well as the quality of erythropoiesis. If iron stores are not sufficient for normal erythropoiesis or if some condition prevents iron from being inserted into hemoglobin during erythropoiesis, the reticulocyte hemoglobin concentration will be decreased.

Disorders that impair iron incorporation during erythropoiesis include anemia of chronic disease (also called anemia of inflammation) and sideroblastic anemia. In one mechanism of the development of anemia of chronic disease, iron release from macrophages is blocked through the action of hepcidin, which is often increased in infection or inflammation. In sideroblastic anemia, enzymes necessary for normal heme biosynthesis are defective or deficient, and iron is not fully inserted into hemoglobin. Lack of iron and functional iron defects both result in decreased hemoglobin content in reticulocytes.
Conversely, the reticulocyte hemoglobin concentration is a sensitive indicator of response to iron therapy: in a positive response it will be increased even before other parameters, such as the hemoglobin and hematocrit, rise. Furthermore, a low reticulocyte hemoglobin content can suggest an iron-deficient state when hemoglobin, hematocrit, and red blood cell indices are normal. Patients receiving erythropoietin may also be monitored for treatment effectiveness by utilizing the reticulocyte hemoglobin content. Increases in this parameter correlate with a positive therapeutic response.

In addition, the reticulocyte hemoglobin concentration has been identified as a specific marker to screen for iron deficiency in infants and to monitor patients receiving hemodialysis. The American Academy of Pediatrics recommends two methods that should be used to screen for possible iron deficiency in infants presenting with a hemoglobin concentration of less than 11.0 g/dl. The first suggested strategy utilizes results of serum ferritin with C-reactive protein testing, while the second screen employs the reticulocyte hemoglobin content. Patients receiving maintenance hemodialysis are often treated with erythropoietin-stimulating drugs and intravenous iron. Therefore, evaluating iron status in these patients provides important information for managing therapy. The reticulocyte hemoglobin content has been shown to be a useful parameter for guiding treatment decisions, especially in patients with end-stage renal disease who are receiving long-term hemodialysis. Finally, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative recommends the reticulocyte hemoglobin concentration assay to establish baseline iron status in patients with chronic renal disease.

**Immature Platelet Fraction**

The immature platelet fraction is another advanced clinical parameter available on automated hematology instruments. It has become an important adjunct test in the evaluation of thrombocytopenia. Thrombocytopenic patients have a high risk for severe bleeding. This condition results from one of two possible mechanisms. Either platelets are not being effectively produced in the bone marrow or they are being inappropriately destroyed as they circulate. In platelet-production disorders such as aplastic anemia or leukemia or the use of marrow-suppressive drugs, the immature platelet fraction will be low or in the normal range. However, in conditions that increase destruction of platelets, including immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, drug effects, or other causes, the immature platelet fraction will be elevated. The immature platelet fraction is most useful when measured serially and evaluated against a concurrent platelet count. Patients who present with thrombocytopenia and a low or normal immature platelet fraction display results consistent with impaired–platelet-production disorders. Patients who have thrombocytopenia and a high immature platelet fraction most likely have a condition related to increased platelet destruction. Identifying the mechanism associated with thrombocytopenia allows the clinician to initiate the most appropriate therapy.
The immature platelet fraction is also useful in assessing platelet recovery after stem cell transplant or chemotherapy. When treatment is successful, an increase in the immature platelet fraction is seen before the platelet count rises. The ability to forecast platelet regeneration based on the immature platelet fraction can potentially reduce the need for prophylactic platelet transfusions in patients who have received stem cell transplants or chemotherapy. Serial immature platelet fraction values are evaluated for increasing trends. If the immature platelet fraction does not rise, the patient is demonstrating a poor platelet response to the therapy and transfusions may be warranted.

Immature Granulocytes

The ability to measure the population of immature granulocytes has greatly enhanced the white blood cell count. Automated leukocyte differential results have been available from hematology analyzers for several years, but this additional data can provide physicians with even more information to evaluate patients who present with a variety of abnormalities, including bacterial infections, inflammatory conditions, trauma, myeloproliferative neoplasms, cancer, tissue necrosis, and acute transplant rejection. The immature granulocyte population has been used as an alternative to the band count in assessing neonates with sepsis. Identifying these conditions is important so that appropriate and timely treatment regimens can be initiated.

The immature granulocyte count includes promyelocytes, myelocytes, and metamyelocytes. Immature granulocytes are not normally present in the peripheral blood of non-pregnant adults. Quantitating immature granulocytes provides a rapid and reliable method to identify these cells. In fact, in some patients, notably those who are myelo-suppressed, the very young, and the elderly, the neutrophil count may not be elevated yet the immature granulocyte population may be increased. Published findings support the high specificity of the immature granulocyte count for infectious processes. However, the low sensitivity also associated with this parameter suggests it should not be used as the only screening indicator for a possible infection.

Other Parameters

Some automated instruments provide additional parameters that have recently been developed and have possible applications in the differential diagnosis of microcytic anemias. These analyzers are capable of measuring red blood cell subpopulations and can detect small changes in the volume and hemoglobin content of individual erythrocytes. New parameters assess the percentage of hypochromic, hyperchromic, microcytic, and macrocytic red blood cells. Measuring the percentage of hypochromic and microcytic erythrocytes is especially useful for demonstrating red blood cells that have not effectively
produced hemoglobin. This information serves as a valuable screening tool that can guide appropriate reflex testing. For example, the percentage of hypochromic erythrocytes indicates the status of iron incorporation into hemoglobin over a span of several months and is therefore a sensitive marker of a possible iron deficiency. Likewise, this parameter will be decreased in patients with β-thalassemia. The lack of effective hemoglobin synthesis in this condition occurs because there are not enough β-globin chains to produce adequate levels of hemoglobin. However, the percentage of microcytic red blood cells is higher in β-thalassemia than the percentage of microcytic erythrocytes in iron deficiency. These red blood cell subpopulation parameters have been utilized to develop algorithms for discrimination of microcytic anemias such as iron deficiency and β-thalassemia.

Summary

The amount of information available from automated hematology analyzers has exploded during the past 20 or more years, reflecting tremendous developments in technology. The new advanced clinical parameters enhance the routine complete blood cell count in all cell lineages to include leukocytes, erythrocytes, and platelets. Incorporation of these parameters has documented value in improving patient outcomes.

References


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