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Automated hematology and radiology synergy in diagnosing anemia in children

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***Abstract*---**Aim: This review aims to evaluate the role of automated hematology analyzers and radiological imaging techniques in the diagnosis and management of anemia in children, highlighting traditional and advanced parameters. Methods: A comprehensive literature review was conducted, focusing on automated hematological parameters such as hemoglobin, RBC indices, reticulocyte counts, and novel metrics from modern analyzers, alongside radiological assessments such as bone marrow imaging and organ evaluation. The quasi-morphological approach, reticulocyte kinetic analysis, and imaging technologies like digital imaging and artificial intelligence were examined. Results: Traditional parameters, including RDW and MCV, provide initial insights into anemia classification. Advanced metrics, such as reticulocyte hemoglobin content and immature reticulocyte fractions, improve iron status assessment and therapeutic response evaluation. Radiological imaging offers valuable insights into bone marrow activity and organ health, complementing hematological findings. The use of automated analyzers and imaging techniques demonstrates high reproducibility and rapid results, though challenges in standardization persist. Conclusion: Automated hematology analyzers and radiological imaging techniques significantly enhance the diagnostic landscape for pediatric anemia, yet clinical integration and ongoing refinement of reference ranges are essential. Future developments in technology and standardization may further elevate the efficacy of anemia management in children.

***Keywords*---**Pediatric anemia, automated hematology analyzers, radiological imaging, reticulocyte count, iron deficiency, artificial intelligence.

Introduction

Children's anemia is a very common clinical problem, especially in underdeveloped countries. It occurs in almost all pediatric subspecialties and has many different causes, both obvious and mysterious. Usually, when a kid exhibits indications of anemia such as pallor, lethargy, activity intolerance, ness other symptoms, the automated blood count is the first laboratory test done. Hemoglobin (Hb) and red blood cell (RBC) indices, such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW), are the commonly available and tried-and-true metrics for assessing anemia. A reticulocyte count and peripheral smear are frequently added to these. Numerous new parameters are now available due to the introduction of sophisticated automated analyzers with modern technology. These measures can properly reflect different disease processes and are frequently generated during the hemogram at little or no additional cost. However, there is a lack of uniformity across manufacturers, it can be difficult to get reference ranges, and interpretation outside of controlled trials can be challenging. As a result, clinical practice's acceptance of these more recent standards has not kept up with the expectations outlined in published literature. This review starts with a brief synopsis of the methods now used to diagnose anemia using parameters that are widely available, then it looks at ways to make their assessment better. After that, it talks about the newer and/or more sophisticated automated parameters, highlighting how pediatric practice can use them.

The reference ranges for red blood cell count (RBC), hematocrit (Hct), and hemoglobin (Hb) in children change considerably with age and, to a lesser degree, with race and ethnicity. Gender differences become noticeable as people become older, usually between the ages of 10 and 12. As a result, it is essential to evaluate hemoglobin using the relevant normal range, which is accessible globally (1). Hospital information systems are being implemented in more laboratories, making this procedure easier for clinicians to understand. The appropriate age and gender-specific reference ranges can be electronically chosen by these systems and included in the resultant reports. The majority of studies advise using the less than 2.5th centile for age, ethnicity, and gender, despite the fact that there is continuous debate in the literature on the cut-off percentile for Hb (2.0, 2.5, or even 5th centiles) to diagnose anemia (2).

Traditional Automated Analyzer-Based Methods for Anemia Treatment

After hemoglobin (Hb) estimation and/or clinical diagnosis of anemia, data from automated hematology analyzers can quickly shed light on the cause of the condition. Since the differential diagnosis for pancytopenia or bicytopenia is wider than that for isolated anemia, one of the most important factors to consider is the quantity of cell lines involved. When a blood film or bone marrow examination is required, expeditiously ruling out hematological malignancy supersedes additional anemic work-up in the right clinical setting. Following this first assessment, isolated anemia is usually best treated by utilizing two widely accepted methods for hemogram data analysis, which are frequently utilized in tandem with the patient's history and physical examination results:

Quasi-Morphological Approach

Using the red cell distribution width (RDW) as a proxy for blood film evaluation, this method uses the mean corpuscular volume (MCV) and the degree of red cell anisocytosis to classify anemias. As a result, the patient may have anisocytosis or microcytic, normocytic, or macrocytic anemia when they first arrive. To further refine differential diagnoses, the mean corpuscular hemoglobin (MCH) is also assessed as a hypochromia indication (3). In the context of red cell distribution width (RDW) and mean corpuscular volume (MCV), various conditions can be categorized as follows:

Normal RDW:

- **Low MCV:** Typically associated with thalassemia traits (α, β, δβ thalassemia), Hb Lepore, and HbE traits. It may also indicate conditions like iron deficiency anemia or anemia of chronic disease (ACD), which can be influenced by long-standing inflammation or malignancy.
- **Normal MCV:** Reflects a normal state or may indicate early or latent iron deficiency, multiple-deficiency anemia, acute blood loss, hemolytic anemia due to enzymopathies or keraunopathies (such as G6PD deficiency), sickle cell anemia, immune hemolysis, or recent transfusions.
- **High MCV:** Can be linked to aplastic anemia, inherited marrow failure syndromes, hypothyroidism, liver disease, or certain forms of myelodysplastic syndromes (MDS).

High RDW:

- **Low MCV:** Suggests thalassemia major or intermedia, HbH disease, and sideroblastic anemia, along with conditions such as microangiopathic hemolysis (including hereditary pyropoikilocytosis) or deficiencies of vitamins C and E, copper, and aceruloplasminemia.
- **Normal MCV:** Associated with early iron deficiency, post-chemotherapy recovery, or acute blood loss.
- **High MCV:** Often indicative of megaloblastic anemia, RBC agglutination, or hemolytic anemia characterized by marked reticulocytosis.

Reticulocyte Count-Based Estimation of Red Cell Kinetics:

Most 5-part and more sophisticated analyzers can easily provide the reticulocyte count. Erythropoietic activity in the bone marrow is correlated with the proportion of red blood cells that contain reticulocytes. Cases of anemia can be divided into two groups based on the reticulocyte count: (1) cases with an appropriate response to anemia (e.g., anemia from hemolysis, acute or chronic blood loss, transient marrow suppression followed by nearly immediate recovery), and (2) cases with an inappropriately low response (e.g., very low counts in marrow aplasia, pure red cell aplasia, drug/radiation-induced suppression, and moderately low to near-normal counts in micronutrient deficiencies and dyserythropoietic anemias) (4–10). Patients with severe reticulocytosis and normal hemoglobin present a distinct case of compensated hemolysis, usually

represented by milder forms of hereditary spherocytosis and certain rare enzymopathies. Individuals who have myelophthisis, such as myelofibrosis or metastases, also have higher than normal reticulocyte numbers. When the data from these two methods are combined with the clinical background, it is typically possible to determine the cause of the anemia with some degree of accuracy. Furthermore, red cell histogram analysis can occasionally be useful.

Analysis of the Red Blood Cell Volume Histogram:

The mean corpuscular volume (MCV) and red cell distribution width (RDW) are directly obtained from the red blood cell size frequency distribution histogram, which usually has a symmetrical or Gaussian form. Uniform microcytosis with absolute or relative erythrocytosis is a noteworthy unique example. It is commonly known that α- or β-thalassemia trait is indicated by a constellation of data that includes reduced MCV, normal RDW, raised RBC count (absolute or relative to Hb), and usually reduced mean corpuscular hemoglobin (MCH) (11,12). Comparable outcomes can also be observed in traits related to δβ-thalassemia, HbE, and Hb Lepore, as well as in ailments such as iron-deficient polycythemia vera, iron deficit during treatment, and cyanotic congenital heart disease (12,13). The RDW is a crucial component of both the red cell histogram analysis and the quasi-morphological approach. The RDW is available from contemporary analyzers as both the standard deviation (SD) and the coefficient of variation (CV).

Different Histogram Types:

1. A normal Gaussian curve indicates no abnormalities.
2. A peak with normal width shifted to the left suggests uniform microcytosis, often seen in individuals with β- or α-thalassemia trait.
3. A peak with increased width shifted to the right indicates conditions such as megaloblastic anemia, marked reticulocytosis, or mild RBC agglutination.
4. An extension or failure of the curve to touch the baseline on the left side denotes the presence of smaller RBCs merging into platelets, which can be seen in conditions with very small RBCs like microspherocytic or fragmented RBCs, or the presence of macrothrombocytes or platelet clumps.
5. A right “shoulder” or trailing of the erythrocyte population to the extreme right is indicative of extremely large RBCs (macrocytes), marked red cell agglutination, or a significant increase in reticulocytes.
6. The presence of two populations of red cells can be observed in heterozygotes for X-linked sideroblastic anemia or individuals who have received transfusions from carriers of β-thalassemia trait or HbE.

How to Decide Between RDW-SD and RDW-CV:

Although they take different approaches to this, RDW-CV and RDW-SD are both measurements of the dispersion of RBC volumes around their m. RDW-CV calculates the dispersion as a ratio between the MCV and one standard deviation (SD). Changes in the SD or MCV therefore affect the outcomes. Whereas macrocytosis tends to lower the RDW-CV by raising the MCV, microcytosis tends to raise it by decreasing the denominator (MCV). Consequently, in cases of excessive microcytosis, RDW-CV may be erroneously high, and in cases of macrocytic anemia, it may be mistakenly normal (12, 14). However, corpuscles

below this threshold, such as aperture artifacts, cell coincidence errors (doublets, triplets, etc.), and agglutinates on the right extreme, as well as platelet clumps, electrical interference, and very large platelets on the left, are not included in the RDW-SD measurement of the RBC histogram width at the 20% height level. RDW-SD is a more dependable measure of dispersion than RDW-CV because it is not dependent on MCV; this is especially true for patients with aberrant MCVs (12, 14).

Advanced Parameters for Anemia and Red Cell Analysis

This section addresses selected recently developed important parameters, focusing on the clinical applications of analyzer data rather than its technological derivation and instrumentation.

Diagnosis of Iron Status (Iron Deficiency and Iron-Restricted Erythropoiesis) by Automated Hematology Analyzers

Assessment of iron status is crucial not only for children with suspected iron deficiency but also for those in whom iron deficiency may coexist with acute or chronic inflammatory states or chronic diseases such as chronic kidney disease (CKD), inflammatory bowel disease (IBD), hemophagocytic lymphohistiocytosis (HLH), and pediatric rheumatological illnesses. Conventional red cell indices (MCV, MCH, MCHC, RDW) are not sensitive enough in the early or latent stages of iron deficiency and do not change rapidly enough to predict the response to iron therapy in deficient patients. Furthermore, these indices are not useful in distinguishing coexisting iron deficiency in inflammatory states (15).

Reticulocyte Hemoglobin Content (CHr) and Reticulocyte Hemoglobin Equivalent (Ret-He):

Modern automated hematology analyzers incorporate several parameters to measure the iron content of circulating erythrocytes, the most effective of which reflect the availability of iron to erythroid precursors. CHr, measured by Siemens and Abbott analyzers, quantifies hemoglobin mass in reticulocytes, directly dependent on iron bioavailability. Given the short maturation time of reticulocytes into erythrocytes (typically 1-2 days), the hemoglobin content of these newly-released immature erythrocytes reflects the short-term dynamics of iron availability for erythropoiesis in the bone marrow. RET-He (Sysmex analyzers) is a related biomarker serving essentially the same purpose (12,15,16). Both CHr and Ret-He are physiologically appropriate indicators of iron status in pediatric CKD, as the synthesis of iron-replete reticulocytes is highly dependent on erythropoietic iron bioavailability. Additional advantages include lower cost compared to conventional tests and the requirement for a lower blood sample volume, as analysis is typically performed on the same EDTA specimen used for the hemogram (12,15,16). An alternative approach to diagnosing iron deficiency or iron restriction is to assess the response to therapy of the immature reticulocyte fraction, which is discussed in the next section.

Newer Factors Related to Microcytosis and Hypochromia:

The percentages of hypochromic and microcytic RBCs (Siemens, Abbott, and Sysmex) and related parameters such as low hemoglobin density (LHD%) and red cell size factor (RSF) (on Beckman Coulter instruments) at various thresholds can be sensitive indicators of both iron deficiency and iron-restricted erythropoiesis. LHD% is a potential marker of iron availability provided by Beckman Coulter analyzers and is derived from the mean cell hemoglobin concentration using the mathematical sigmoid transformation. Red blood cell size factor (RSF) is a new parameter provided by Beckman Coulter, combining the volume of erythrocytes and the volume of reticulocytes. RSF is a potential screening parameter for evaluating patients with hypochromic microcytosis and identifying possible cases of α-thalassemia trait regardless of iron status. However, there may be interference in cases with inherited forms of hypochromic microcytosis, as the frequencies of β- and α-thalassemia and HbE trait are significant (11,17). Hence, interpretation of the complete blood count is recommended, preferably with full knowledge of the specific clinical setting. These factors also depend on the time of sample processing. For example, the 2016 update to the National Institutes of Clinical Excellence (NICE) guidelines for assessing iron status in CKD patients states that the percentage of hypochromic red cells (%HRC), CHr, or Ret-He are superior to serum ferritin alone in predicting therapeutic response to intravenous iron. %HRC should be used if testing is possible within six hours; otherwise, CHr or Ret-He should be used (18). Although Ret-He is reduced in both iron deficiency and thalassemia trait, formulae incorporating novel RBC indices have been designed to distinguish these conditions. For instance, an "Urrechaga Index" uses a cut-off of greater than minus 7.6 on the formula "% MicroR - %Hypo-He - RDW" to recognize heterozygous thalassemia with 100% sensitivity and 92.6% specificity. Values greater than minus 7.6 are highly suggestive of heterozygous β-thalassemia, which must then be confirmed by estimating the HbA2 percentage (19,20).

Parameters Based on Reticulocyte Subclassification
Fraction of Immature Reticulocytes (IRF)

The ratio of immature, young reticulocytes to total reticulocytes is represented by the IRF. Reticulocyte RNA is stained by analyzers using fluorescent or nonfluorescent dyes (such as thiazole orange, Oxazine 750, and new methylene blue). The reticulocyte count and IRF are measured using a combination of fluorescence and narrow-angle laser light scatter to identify the red blood cells. Even though the majority of these dyes also stain DNA, leukocytes have much more DNA than reticulocytes do RNA, making it simple to separate the two based on differences in fluorescence intensity (4,5,12,16). Based on the intensity of their fluorescence emission, reticulocytes can be classified into three subsets: the most immature, moderately immature, and mature reticulocytes. The reference range of the IRF, which normally ranges from 2.0% to 16.2%, comprises the most immature and moderately immature reticulocytes (12). In clinical terms, severe aplastic anemia or renal failure are indicated by a low IRF combined with a low reticulocyte count. On the other hand, athletes with hemolysis, hematinic response, and erythropoietin doping have a high IRF along with a high reticulocyte count. As with myelodysplastic syndromes or congenital dyserythropoietic anemia, dyserythropoiesis is suggested if the IRF is inexplicably high with a low reticulocyte count. After myeloablative chemotherapy, engrafting

marrow and hematopoietic regeneration may result in a high IRF with a normal reticulocyte count. Thus, the IRF can be used to measure the hematinic response in combination with Ret-He, and to track marrow regeneration (engraftment) following transplantation or chemotherapy. Following marrow ablation therapy, the first erythropoietic response is an increase in IRF, which occurs a few days ahead of the rise in reticulocyte count and absolute neutrophil count (ANC) (4,5,12,16).

Fragmented RBC Enumeration

The detection of fragmented red blood cells (FRCs) is crucial for diagnosing thrombotic microangiopathy, a condition often considered a medical emergency. Manual assessment of FRCs is prone to interobserver bias, and similar cells can appear in membrane/hemoglobin-related hemolytic disorders and in patients undergoing dialysis, which can affect specificity. Automated enumeration of FRCs offers advantages such as rapid results, high reproducibility, and reasonably good concordance with microscopy (12,26). Modern analyzers (Siemens, Sysmex) use fluorescent flow cytometry to measure FRCs in the reticulocyte channel through proprietary algorithms. These cells occupy a region beneath the RBC population in the scattergram and exhibit extremely low side fluorescence signals due to the absence of ribonucleic acids in mature RBCs and a high-angle forward scatter (FSC). Automated FRC counts generally have high negative predictive values, meaning cases with less than 1% schistocytes on automated counts are unlikely to reveal these cells on smear evaluation. However, they show poorer specificity in cases with higher counts, particularly in iron deficiency and megaloblastic anemias. Therefore, it is essential to correlate these findings with the clinical context, platelet and reticulocyte counts, and ultimately, a peripheral smear in cases with elevated FRC% (5,12).

Spurious Results and Pitfalls in Automated Analyzers

Automated red cell analysis and the diagnosis of anemia necessitate familiarity and experience with the specific analyzer being used, as well as an understanding of normal patterns and ranges for both the instrument and the patient population (8,29-32). From a laboratory perspective, errors can be categorized into pre-analytical, post-analytical, and analytical phases.

Future Directions

Significant advances in automated approaches to anemia diagnosis have occurred over the past decade. Future progress is anticipated in the realms of digital image analysis and artificial intelligence. The commercially available CellaVision™ software, for instance, scans and "reads" Romanowsky-stained slides to offer standardized RBC morphology reporting with minimal manual supervision. This software has demonstrated highly promising results in screening for schistocytes, intra-erythrocytic parasites, and inclusions, and as a modality for identifying inherited hemolytic anemias (33). Additionally, computer-aided artificial intelligence systems have been developed for RBC classification in smear images. These models are capable of evaluating significantly larger cell numbers than

manual analyses, detecting subtle abnormalities invisible to the human eye, and improving over time through training (34-36).

Main Role of Radiologist

Radiologists play a crucial role in the multidisciplinary approach to diagnosing and managing pediatric anemia. By utilizing advanced imaging techniques, radiologists provide essential insights into bone marrow activity, organ health, and potential underlying causes of anemia. Their expertise in interpreting radiological images complements the data obtained from automated hematology analyzers, offering a more comprehensive diagnostic picture. This collaborative effort between hematology and radiology ensures accurate diagnosis, effective treatment planning, and better patient outcomes, particularly in complex or atypical cases of anemia in children.

Conclusion

In summary, anemia in children remains a prevalent and multifaceted issue, particularly in underdeveloped regions where access to healthcare is limited. This review underscores the importance of automated hematology analyzers and radiological imaging in diagnosing and managing pediatric anemia. Standard hematological parameters such as hemoglobin levels, RBC indices (MCV, MCH, MCHC, RDW), and reticulocyte counts provide foundational insights into anemia's etiology. The quasi-morphological approach, utilizing RDW and MCV, allows clinicians to classify anemias effectively, while reticulocyte count aids in understanding bone marrow response to anemia. Advanced automated parameters, including reticulocyte hemoglobin content and immature reticulocyte fractions, enhance diagnostic accuracy for iron status and response to therapy, offering valuable information in complex clinical scenarios like chronic inflammatory states and concurrent anemia. Radiological imaging, particularly bone marrow imaging and organ evaluations, complements hematological findings by providing a comprehensive view of the patient's condition, aiding in the differentiation of anemia types and the detection of underlying causes. New technologies in digital image analysis and artificial intelligence promise to refine both hematological and radiological assessments, facilitating more accurate diagnoses with reduced manual oversight. Despite these advancements, variability among analyzer manufacturers and the lack of standardized reference ranges present challenges in clinical practice. Therefore, integrating these automated methods and imaging techniques with clinical judgment and comprehensive patient history is vital for effective anemia management. Future research should focus on standardizing these approaches and further investigating the clinical utility of emerging parameters and imaging techniques, ultimately aiming to improve outcomes for children with anemia.

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