

Hematologic Emergencies: Acute Anemia

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Anemia can be seen in the emergency department both as a primary pathological process or secondary to both medical and surgical diseases. Moreover, acute anemia can occur in children who have been otherwise healthy, who have systemic disease, or who have known hematologic disorders. Anemia may indicate a disorder with a single hematopoietic cell line (eg, red blood cells) or may be associated with changes in multiple cell lines indicative of bone marrow involvement, immunologic disease, peripheral destruction of erythrocytes, or sequestration of cells. Independent of the etiology, prompt diagnosis is predicated on understanding the classifications of anemia, the associated presenting symptoms, and the proper ordering and interpretation of laboratory studies. This article will discuss the evaluation, proper classification, differential diagnosis, and initial management of acute anemia using cases representative of those that might be seen in the pediatric emergency department.

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“The are cases . . . in which [the blood’s] amount of globules falls much below the physiological mean, and diminishing more and more, reaches a proportion so low that we can scarcely comprehend how, with so few globules in the blood, life can still be maintained.” — Gabriel Andral, 1843 [1]

Definition

Anemia is defined as a reduction in red blood cell (RBC) mass or blood hemoglobin (Hb) concentration resulting in a decrease in the oxygen-carrying capacity of the blood. Because the Hb value is measured directly using today’s automated hematology analyzers, it is considered more accurate than the hematocrit, which used to be directly measured but is now usually calculated from the RBC count and mean corpuscular volume (MCV) [2]. In addition, the Hb concentration relates more directly to oxygen-carrying capacity, and as such will be the preferential measurement referred to in this review. The definition of anemia is a Hb concentration 2 standard deviations (SD) below the mean Hb for the child’s age. As illustrated (Table 1), Hb concentration varies with age, with higher values being present in the newborn. Immediately after birth, a decrease in erythropoietin

production occurs in response to a rise in arterial PO₂. This results in a slow drift downward to a physiological nadir in Hb between 6 and 8 weeks of life. Term infant Hb concentrations fall to 9 to 11 g/dL over the first few months of life and preterm infant Hb concentrations can be as low as 7 to 9 g/dL. In addition, with regard to preterm infants, it should be noted that values typically reported for the neonatal period refer to term infants. Premature infants have less time *in utero* to synthesize RBCs and as such are typically born with a lower Hb concentration. In addition to variability because of age, the range of normal Hb concentrations also varies based on sex. Furthermore, differences in ethnicity may be reflected in Hb concentration mirroring the incidence of α -thalassemia in these populations leading to slightly lower Hb concentration [3].

It should be noted that using the definition of 2 SDs as the lower limit of the reference ranges of Hb classifies up to 2.5% of the normal population as anemic. As such, one should appreciate that relying strictly on a statistical definition of anemia may overlook or obscure significant physiological features, such as healthy children with a

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Table 1 Normal mean values for hemoglobin, hematocrit, and MCV.

| Age (y) | Hemoglobin (g/dL) | | Hematocrit (%) | | MCV (μ L) | |
|------------|-------------------|-------------|----------------|-------------|----------------|-------------|
| | Mean | Lower Limit | Mean | Lower Limit | Mean | Lower Limit |
| Cord blood | 16.5 | 13.5 | 51 | 42 | 108 | 98 |
| 1 wk | 17.5 | 13.5 | 54 | 42 | 107 | 88 |
| 2 wk | 16.5 | 12.5 | 51 | 39 | 107 | 86 |
| 1 mo | 14.0 | 10.0 | 43 | 31 | 104 | 85 |
| 2 mo | 11.5 | 9.0 | 35 | 28 | 96 | 77 |
| 3-6 mo | 11.5 | 9.5 | 36 | 29 | 91 | 74 |
| 0.5-1.9 | 12.5 | 11.0 | 37 | 33 | 77 | 70 |
| 2-4 | 12.5 | 11.0 | 38 | 34 | 79 | 73 |
| 5-7 | 13.0 | 11.5 | 29 | 35 | 81 | 75 |
| 8-11 | 13.5 | 12.0 | 40 | 36 | 83 | 76 |
| 12-14 | | | | | | |
| Female | 13.5 | 12.0 | 41 | 36 | 85 | 78 |
| Male | 14.0 | 12.5 | 43 | 37 | 84 | 77 |
| 15-17 | | | | | | |
| Female | 14.0 | 12.0 | 41 | 36 | 87 | 79 |
| Male | 15.0 | 13.0 | 46 | 38 | 76 | 78 |
| 18-49 | | | | | | |
| Female | 14.0 | 12.0 | 42 | 37 | 90 | 80 |
| Male | 16.0 | 14.0 | 47 | 40 | 90 | 80 |

Data from Oski FA, Brugnara, C, Nathan, DG. *A diagnostic approach to the anemic patient*. In: Nathan, DG, Orkin, SE, Ginsburg, D, Look, AT, editors. *Nathan and Oski's hematology of infancy and childhood*. Philadelphia: WB Saunders Company; 2003. p. 409.

“statistical anemia” [4] or children with a normal Hb for age but a “relative anemia” as in the case of underlying cyanotic congenital heart disease where they ought to have a higher Hb [5].

Classification of Anemia

Anemia is traditionally classified according to either the underlying pathophysiologic process (Table 2) or the RBC size (Table 3). The pathophysiologic approach begins with 2 broad categories: failure of RBC production, and increased RBC loss or destruction. The former includes decreased production due to bone marrow failure, impaired erythropoietin production, and disorders of RBC maturation. The latter includes the hemolytic anemias, red cell membrane and metabolic defects, and direct injury to RBCs. The 2 classifications are not mutually exclusive, in that more than one mechanism may be present in some anemias, but typically one functional disorder is the underlying cause for the patient's anemia. Furthermore, classification based on pathophysiologic mechanism is coupled with erythrocyte size (microcytic, normocytic, or macrocytic) and morphology. This, combined with data from the history and physical examination, allows the clinician to narrow the focus of the initial differential diagnosis. Of note, blood loss secondary to trauma, nontraumatic hemorrhage such as an upper gastrointestinal bleed or severe nosebleed or chronic menorrhagia, represents a major cause of acute anemia seen in pediatric patients in the emergency department (ED). The diagnosis and management of

acute hemorrhage in pediatric patients has been well covered in a variety of excellent texts and the reader should refer to these sources as necessary [6].

Diagnostic Evaluation

In many cases, anemia is a sign of underlying disease and not a final diagnosis in and of itself. As such, the goal of the diagnostic evaluation of the patient is to determine the underlying cause of the anemia. The initial approach to an anemic patient includes a detailed history and physical examination, along with a panel of essential laboratory tests. The examiner should be aware of historical factors that can be of particular help in uncovering the etiology of anemia. For anemia in early infancy, a maternal history should elicit any complications with the pregnancy or delivery, maternal drug ingestion, pica, and anemia during pregnancy. In all patients, a detailed family history should be obtained with attention paid to ethnicity, a history of anemia, jaundice, splenomegaly, bleeding diatheses, malignancy, and transfusions. The patient's past medical history should be evaluated for hyperbilirubinemia, diet, medications, activity level, acute or chronic infections, endocrinopathies, and easy bruising or blood loss. The physical examination, although important, is frequently unremarkable in children with mild anemia. On the other hand, children with acute anemia often present dramatically with clinical findings that can include tachycardia, tachypnea, delayed capillary refill, icterus, pallor, lymphadenopathy, hepatomegaly or splenomegaly, hematuria,

Table 2 Classification of anemia by pathophysiologic mechanism.

| |
|--|
| I. Failure of erythrocyte production |
| A. Bone marrow failure |
| 1. Aplastic anemia (congenital or acquired) |
| 2. Pure red cell aplasia |
| a. Diamond-Blackfan anemia (congenital) |
| b. Transient erythroblastopenia of childhood (acquired) |
| 3. Marrow replacement |
| a. Malignancies |
| b. Osteopetrosis |
| c. Myelofibrosis |
| B. Impaired erythropoietin production |
| 1. Chronic renal disease |
| 2. Hypothyroidism, hypopituitarism |
| 3. Chronic inflammation |
| 4. Protein malnutrition |
| 5. Hb mutation with decreased affinity for oxygen |
| C. Disorders of erythroid maturation/ineffective erythropoiesis |
| 1. Abnormalities of cytoplasmic maturation |
| a. Iron deficiency |
| b. Thalassemia syndromes |
| c. Lead poisoning |
| d. Sideroblastic anemia |
| 2. Abnormalities of nuclear maturation |
| a. Vitamin B ₁₂ deficiency |
| b. Folic acid deficiency |
| c. Thiamine-responsive megaloblastic anemia |
| d. Hereditary abnormalities in folate metabolism |
| 3. Congenital dyserythropoietic anemia |
| 4. Erythropoietic protoporphyria |
| II. Increased RBC loss or destruction |
| 1. Hemoglobinopathies (including structural and synthetic mutants) |
| 2. Red cell membrane defects |
| 3. Red cell metabolic defects |
| 4. Antibody-mediated |
| 5. Mechanical injury to the erythrocyte |
| 6. Oxidant-induced injury to the erythrocyte |
| 7. Infectious agent-induced red cell injury |
| 8. Paroxysmal nocturnal hemoglobinuria |

and/or evidence of congestive heart failure. The astute clinician should also realize that anemia is commonly an incidental finding that occurs during a routine evaluation of an otherwise well child, or an unexpected finding during the examination of child with an acute illness. Similarly, clinicians should be aware that laboratory artifact can inadvertently lead to a diagnosis of anemia. Technical errors in the determination of the hematocrit such as plasma trapping [7], inadequate centrifugation, or use of capillary samples can lead to an underestimation of the hematocrit [8]. In these cases, the laboratory finding of anemia may be incongruous with the data from the history and physical examination. Keeping these pitfalls in mind when considering all of the diagnostic data will allow the clinician to avoid the injudicious use of laboratory tests.

Historical Factors of Importance in Evaluating Patients With Anemia

A variety of historical factors can be elicited during a detailed evaluation of the patient that can provide clues to the etiology of anemia including age, sex, race, ethnicity, diet, medication use, symptoms indicating infection, and family history. For example, anemia detected in patients between the ages of 3 to 6 months is suggestive of a congenital disorder of Hb structure or synthesis, as opposed to nutritional iron deficiency, which is almost never responsible for anemia in term infants before 6 months of age [9]. It is also important to bear in mind that anemia during the neonatal period may have isoimmunization from maternal antibodies or a congenital hemolytic anemia, along with recent blood loss, within the differential diagnosis. A neonatal history of hyperbilirubinemia may be an important clue in the diagnosis of a congenital hemolytic anemia later in childhood, such as hereditary spherocytosis, which is also supported by a family history of anemia, splenectomy, and/or cholecystectomy. Certain hematologic disorders

Table 3 Classification of anemia based on red cell size.

| |
|---|
| I. Microcytic anemia (MCV < 70 fL + years of age) |
| 1. Iron deficiency |
| 2. Drug/toxin-mediated (including lead poisoning) |
| 3. Thalassemia syndromes |
| 4. Chronic inflammation |
| 5. Sideroblastic anemias |
| II. Normocytic anemia |
| 1. Congenital hemolytic anemias |
| a. Hemoglobinopathies |
| b. Red cell enzyme defects |
| c. Red cell membrane defects |
| 2. Acquired hemolytic anemias |
| a. Antibody-mediated |
| b. Microangiopathic hemolytic anemias |
| c. Anemia secondary to acute infection |
| 3. Acute blood loss |
| 4. Chronic renal disease |
| 5. Splenic sequestration |
| III. Macrocytic anemia (MCV > 84 fL + 0.6 × yrs of age) |
| 1. With megaloblastic bone marrow (disturbance of DNA synthesis) |
| a. Vitamin B ₁₂ deficiency |
| b. Folic acid deficiency |
| c. Thiamine-responsive megaloblastic anemia |
| d. Drugs (eg, methotrexate, certain anticonvulsants) |
| 2. Without megaloblastic bone marrow |
| a. Aplastic anemia |
| b. Diamond-Blackfan anemia |
| c. Hypothyroidism/hypopituitarism |
| d. Liver disease |
| e. Bone marrow infiltration |
| f. Congenital dyserythropoietic anemia |

leading to anemia are X-linked and therefore seen exclusively in males, including glucose-6-phosphate dehydrogenase (G6PD) and pyruvate kinase deficiencies, both lead to hemolytic anemias [10]. Similarly, enzyme deficiencies and hemoglobinopathies are more common in certain ethnic populations such as disease associated with Hb S and C in Africans or African Americans, and G6PD deficiency and thalassemia syndromes in patients of Mediterranean origin. Many of the hemoglobinopathies and enzyme deficiencies that can lead to anemia are inherited; therefore, it is crucial to ask about a family history of hematologic diseases as well as a history of jaundice, gallstones, or splenomegaly.

Because effective erythropoiesis is dependent on an adequate intake of iron, vitamin B₁₂, and folic acid, it is essential to inquire about dietary or feeding habits. Unusual eating behaviors such as pica or pagophagia (ice eating) may indicate iron deficiency anemia [11]. Attention should be paid to any medications being taken by a patient being evaluated for anemia. A wide variety of drug classes are capable of inducing antibodies that are then capable of destroying circulating RBCs. These include antibiotics such as the penicillins and sulfa drugs, neuroleptics, including tricyclic antidepressants and phenothiazines, cardiovascular drugs including thiazide diuretics and α -methyl dopa, and antihyperglycemics of the sulfonylurea class. In patients with G6PD deficiency, infection or the use oxidant drugs such as the antimalarial drugs primaquine and chloroquine, sulfonamides, or a variety of other medications, can trigger an acute hemolytic episode [12].

Anemia can also accompany a variety of acute as well as chronic diseases. Diarrheal illnesses are commonly seen in the ED. In cases of long-standing diarrhea and macrocytic anemia, one should consider small bowel disease leading to malabsorption of folate or vitamin B₁₂. Alternatively, inflammatory bowel disease and exudative enteropathies can lead to acute blood loss and subsequent microcytic anemia. These patients can also have the normocytic anemia associated with chronic inflammation. Recent studies have shown that release of inflammatory mediators such as interleukin-6 can trigger an increased production of hepcidin, a 25-amino acid peptide produced in the liver. Hepcidin inhibits iron absorption in the small intestine and causes sequestration of iron in macrophages. This cascade is thought to be responsible for the normocytic anemia associated with chronic disease and inflammation [13].

Physical Findings as Clues to the Etiology of Anemia

Pallor is the most common symptom associated with anemia and is due to the combination of the concentration of Hb in the blood, the state of vasoconstriction

of cutaneous blood vessels, and the presence or absence of edema. Pallor as a physical finding is variable, as many children appear pale despite a normal Hb concentration. Similarly, a “sallow” or slightly yellowish complexion may be familial and not necessarily indicative of anemia or hemolysis. In addition to pallor, a variety of other physical findings are associated with anemia, including headache, faintness, weakness, fatigue, irritability, tachycardia, dyspnea, anorexia, and edema. Children with hemolytic anemia may experience nausea, vomiting, abdominal pain, joint pain, fever, jaundice, and a change in the color of the urine. Interestingly, despite the apparent ease with which one might seem to be able to detect these symptoms, the degree of anemia measured by the laboratory is not well predicted by physicians [14]. Other physical examination findings may serve as important clues to the etiology of anemia. For example, examination of the face can demonstrate the frontal bossing and maxillary prominence occasionally seen with extramedullary hematopoiesis in thalassemia major [15] or rarely in severe iron deficiency anemia. Angular stomatitis is frequently seen in iron deficiency anemia, as is the glossitis that characteristically accompanies B₁₂ or folate deficiency. Patients with congenital hemolytic anemia or leukemia can have marked splenomegaly.

Laboratory Evaluation

The initial laboratory evaluation should include a complete blood cell (CBC) count with measurement of the RBC indices, white blood cell (WBC) count with differential, reticulocyte count, and the preparation and examination of a peripheral blood smear. Appropriate care should be taken when obtaining the sample to avoid spurious results. A sample of adequate volume should be obtained, thus avoiding excessive dilution by the anticoagulant present in the collection tube. The measured Hb should be compared with normal values for children of the same age and sex (Table 1) to ensure that the child is truly anemic before embarking on an extensive laboratory evaluation.

Once it is determined that a child is anemic, it is important to examine the red cell indices, particularly the MCV. This value allows for classification of anemia by RBC size as microcytic, normocytic, or macrocytic (Table 3). A helpful rule of thumb for children younger than 10 years is that the lower limit for the MCV is approximately 70 fL plus the age in years. The upper limit of MCV is typically 84 plus 0.6 fL per year of age, with the upper limit in adults being 96 fL. Of the other red cell indices, the mean corpuscular Hb concentration (MCHC) is also a valuable parameter in that it reflects cellular hydration status. A high value (>35) is characteristic of spherocytosis, whereas a low value is most commonly seen in iron deficiency anemia [16]. The red cell volume distribution width (RDW) is an index of the variation in red cell size.

A normal RDW (11.5%-14.5%) indicates that a uniform population of RBCs of a similar size exists. This is seen in healthy patients as well as those with β -thalassemia trait, although in the latter the cells are notably microcytic. An elevated RDW indicates a varying population of RBCs (ie, anisocytosis) that may accompany disorders such as iron deficiency, Hb H disease, certain hemoglobinopathies, and red cell fragmentation due to hemolysis [17-19].

Evaluation of the reticulocyte response is also critical in the evaluation of anemia, helping to distinguish impaired erythropoiesis from increased erythrocyte destruction. It should be noted that in cases of acute blood loss, the reticulocyte count is often not elevated for 3 to 4 days; thus, a low value does not always indicate an impaired erythropoietic response. As such, the reticulocyte count is most helpful in cases in which a patient has been anemic for more than a few days. Anemias can be categorized based on the adequacy of the reticulocyte response (Table 4). Because the reticulocyte count is typically reported as a percentage of total RBCs, patients with moderate to severe anemia may have an elevated reticulocyte count that, in absolute terms, is inadequate.

Table 4 Classification of anemia by corrected reticulocyte response.

Corrected reticulocyte count <2%

Microcytic

Iron deficiency anemia

Thalassemia

Lead toxicity

Anemia of chronic disease

Normocytic

Acute infection (eg, parvovirus B19)

TEC

Renal disease

Hypothyroidism

Aplastic anemia (with pancytopenia)

Leukemia (with alterations in other cell lineages)

Macrocytic

Vitamin B₁₂/folate deficiency

Diamond-Blackfan anemia

Fanconi anemia

Corrected reticulocyte count >2%

Blood loss

Hemolysis

RBC membrane defect

RBC enzyme defect

Hemoglobinopathy

Immune-mediated

Infection-mediated

Microangiopathic (eg, DIC, HUS, TTP)

Paroxysmal nocturnal hemoglobinuria

Hypersplenism

Mechanical injury

Wilson disease

DIC, disseminated intravascular coagulation; HUS, hemolytic-uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

Thus, the reticulocyte count must be corrected for the degree of anemia. To calculate the corrected reticulocyte count, one multiplies the patient's reticulocyte count (or percentage) by the product of the patient's Hb divided by the normal Hb for the patient's age. For example, an 11-year-old boy with a viral infection leading to bone marrow suppression may have a Hb of 6.5 and a reticulocyte count of 0.9% giving a corrected reticulocyte count of $0.9 \times (6.5/13.5) = 0.43$, indicating an inadequate erythropoietic response. A corrected reticulocyte count above 2% indicates increased erythrocyte production. An additional parameter, the reticulocyte Hb content (CHr), can also be helpful in determining the origin of anemia. Changes in CHr reflect iron-restricted erythropoiesis [20,21] and as such, a decrease in CHr is one of the strongest predictors of iron deficiency and iron deficiency anemia in childhood. A CHr of less than 26 pg has been shown to have a sensitivity of 83% and specificity of 75% in the diagnosis of iron deficiency anemia [22].

Should the initial assessment not rule out anemia, not provide sufficient laboratory evidence to support the diagnosis, or raise other less common diagnostic possibilities, additional studies may be indicated. Most of these studies, when indicated, are easily obtained through most hospital laboratories or reference laboratories. These include serum ferritin concentration, supravital stains of the erythrocytes, Hb electrophoresis, screening tests for the presence of unstable hemoglobins, direct and indirect Coombs test, a screening test for G6PD deficiency, and an examination of the bone marrow (Table 5). In cases of macrocytic anemia, vitamin B₁₂ and folate levels, as well as thyroid function studies, may be required. In patients with acute anemia, or in cases of severe or symptomatic anemia in which the etiology is not readily apparent and a pediatric hematologist may be consulted, preparation and evaluation of a peripheral smear before transfusion is essential. Red cell morphology and pathological findings seen on the peripheral smear can indicate the etiology of the anemia. In addition, in cases where acute hemolytic anemia is suspected, it is critical to draw several additional samples before any transfusion to allow for further analysis.

Case Presentation 1

A 2-year-old boy presents to the ED for the further evaluation of anemia diagnosed earlier in the day by his pediatrician. The patient had been in his usual state of good health until several days before admission when his mother noted that he had been significantly more irritable and was less likely to play. She observed that for the past day and had been "laying around" without much energy. His mother reported no fever, upper respiratory tract infection symptoms, nausea, or vomiting. She also denied seeing any bruises or rashes. There has been no blood in the diapers and no black or tarry

Table 5 Additional laboratory studies useful in the diagnosis of anemia.

| Laboratory Study | Use | Interpretation |
|-------------------------------------|--|---|
| Serum free hemoglobin | Differential diagnosis of anemia | Increased in intravascular hemolysis (increased destruction of RBCs); decreased in iron deficiency anemia and anemia of chronic diseases |
| Serum ferritin | Diagnosis of iron deficiency or excess, response to iron therapy | Iron deficiency (decreased), anemias other than iron deficiency (increased) |
| Total iron-binding capacity | Differential diagnosis of anemias | Increased in iron deficiency, as well as acute and chronic blood loss; decreased in thalassemia, anemias of infection, and chronic diseases |
| Hemoglobin electrophoresis | Evaluation of hemoglobinopathies | Various hemoglobinopathies (eg, sickle cell disease, sickle cell trait, HbC, thalassemia major) |
| Fetal hemoglobin | Diagnosis of various hemoglobinopathies | Increased in various hemoglobinopathies; hereditary persistence of fetal hemoglobin; acquired aplastic anemia |
| Direct Coombs (antiglobulin) test | Detects antibodies and/or complement on patient's RBC membrane | Most cases of autoimmune hemolysis, drug-induced hemolysis |
| Indirect Coombs (antiglobulin) test | Detects antibodies in a patient's serum | Isoimmunization from previous transfusion, "nonspecific" autoantibodies in acquired hemolytic anemia |
| Serum haptoglobin | Indicator of chronic hemolysis; not recommended for initial evaluation of acute anemia | Increased in conditions with increased ESR and α_2 globulin, aplastic anemia; decreased in hemolytic anemias (intravascular and extravascular) |
| Free erythrocyte protoporphyrin | Screening for iron deficiency | Early iron deficiency (increased), anemia of chronic diseases, chronic lead poisoning; decreased in primary disorders of globin synthesis |
| Serum transferrin | Differential diagnosis of anemias | Increased in iron deficiency anemia; decreased in anemia of chronic disease |
| Bone marrow aspirate and biopsy | Gold standard for evaluation of erythropoiesis | Allows for direct evaluation of erythroid series |

stools. She indicated that the child had been more fussy and cried when awoken for meals. The child's mother called a relative to come and watch the child while she went to the store, and the relative noted that the child was significantly more pale than several months prior when he last saw the child, prompting the visit to their physician. The pediatrician noted the child to be fussy but active, with marked pallor but no stigmata of infection. There were also no petechiae or purpura noted. A CBC obtained in the office demonstrated a marked anemia with thrombocytosis. The child was sent to the ED for further evaluation and management.

On arrival the patient was noted to be thin (10th percentile for weight), pale, but otherwise well appearing. The blood pressure was 90/52, the heart rate was 145 beats per minute, and the respiratory rate was 16 per minute. Physical examination revealed pale palpebral conjunctiva and oral mucosa. There was no cervical lymphadenopathy noted. The lungs were clear to auscultation but a grade

II/VI systolic murmur was appreciated at the left sternal border. Third and fourth heart sounds were not heard. The abdomen was soft and nondistended without hepatomegaly but a spleen tip was felt on deep palpation. Extremities were warm and the capillary refill was less than 2 seconds, but the nail beds were noted to be pale. There was no evidence of edema in the extremities. There were no cutaneous findings noted. A repeat CBC obtained in the ED revealed a WBC of 8700 with a normal differential. The Hb was 4.2 g/dL and the platelet count was 940 000 per microliter. The MCV was 54 fL and the RDW was 17%. The peripheral smear showed microcytosis, marked hypochromia, mild anisocytosis, and polychromasia. The reticulocyte count was 3.4% and the corrected reticulocyte count was 1.2% indicating decreased RBC production.

The differential diagnosis in this 2-year-old child with pallor and marked microcytic anemia is relatively limited and includes iron deficiency, chronic inflammation,

thalassemia, and lead toxicity. Sideroblastic anemias, which are a heterogeneous group of mitochondrial disorders characterized by anemia, reticulocytopenia, ineffective erythropoiesis, and iron-loaded precursor cells (ring sideroblasts), are a rare cause of microcytic anemia in an otherwise healthy child [23]. Of all the aforementioned diagnostic possibilities, iron deficiency anemia is the most likely. In cases of iron deficiency anemia, it is critical that the etiology of the iron deficiency also be uncovered as part of the diagnostic progress. Thus, the history should include questions intended to uncover factors that could lead to low iron stores, inadequate nutrition, or blood loss (Table 6).

In this case, the family history revealed a distant aunt who had anemia when she was pregnant. There was no family history of hematologic disorders, splenectomy, or gallstones at an early age. When asked about the child's

diet, the patient's mother indicated that he drinks milk "all of the time," up to 60 ounces per day. His mother stated that he did not take any vitamins or other nutritional supplements. He has always "been small," around the 10th percentile for weight.

Based on the history and laboratory evaluation, a diagnosis of iron deficiency anemia secondary to excessive cow's milk intake was made, and the patient was started on oral iron supplements after a thorough evaluation found him to be hemodynamically stable. His parents were also advised to limit his milk intake. Follow-up studies by his pediatrician 1 week later showed an RDW of 24% and a reticulocyte count of 16%.

Case Discussion

Iron deficiency is the most common nutritional deficiency seen in children. Despite measures such as the iron fortification of infant formulas and daily vitamin supplement recommendations [24], iron deficiency anemia is still seen in infants, as well as in both school-aged children and young adolescents, although less commonly [25]. Iron deficiency develops primarily as a consequence of inadequate intake, especially during times of increased demand, such as with prematurity or adolescence, or with blood loss. Full-term infants typically have adequate iron stores that can meet the demands of Hb production during the first 4 months of life, but in the absence of sufficient oral iron intake, they are prone to develop iron deficiency in the latter half of their first year. Premature infants, on the other hand, have smaller iron storage pools and can develop iron deficiency earlier than their full-term counterparts. Although iron deficiency usually begins during the first year of life, its manifestation as anemia is most commonly seen during the second year of life. Although iron deficiency anemia can manifest through adolescence, nutritional deficiency is less common in older children and as such one must consider blood loss or iron malabsorption as a cause.

Iron is absorbed by intestinal mucosal cells and is transferred to the transport protein transferrin and subsequently delivered to specific receptors on erythroblasts. The transferrin-iron complex enters the erythrocyte precursor and the iron is transferred to the mitochondria, which inserts the iron into protoporphyrin for it to become heme. The integrity of the intestinal epithelium is of considerable importance in iron homeostasis as seen by the frequency with which iron deficiency can be seen in patients with inflammatory bowel disease and other malabsorption syndromes [26]. Similarly, infants who are younger than 1 year who are fed cow's milk in excess (in this case 2 to 3 times the recommended daily intake of milk) may develop iron deficiency secondary to both the poor iron bioavailability and the occult blood loss that is frequently associated with the protein-losing enteropathy caused by milk intolerance [27].

Table 6 Factors contributing to iron deficiency.

| |
|---|
| I. Decreased iron intake |
| Dietary (eg, cow's milk anemia) |
| II. Increased use |
| Prematurity |
| Low birth weight |
| Multiple gestation |
| Adolescence |
| Pregnancy |
| Cyanotic congenital heart disease |
| III. Impaired absorption |
| Severe prolonged diarrhea |
| Gastrectomy |
| Inflammatory bowel disease |
| Malabsorption syndrome |
| Celiac disease |
| IV. Blood loss |
| Perinatal |
| Placental (eg, placenta previa) |
| Umbilicus (eg, vasa previa) |
| Postnatal |
| Gastrointestinal |
| Secondary to primary iron deficiency anemia |
| Hypersensitivity to cow's milk |
| Anatomic gut lesions (eg, Meckel diverticulum, colitis) |
| Exudative enteropathy secondary to underlying bowel disease |
| Gastritis (eg, NSAID use) |
| Intestinal parasites (eg, hookworm) |
| Henoch-Schonlein purpura |
| Respiratory tract/pulmonary |
| Epistaxis |
| Pulmonary hemosiderosis |
| Goodpasture syndrome |
| Renal |
| Hematuria |
| Nephrotic syndrome (loss of transferrin) |
| Genitourinary (eg, menstruation) |

NSAID indicates nonsteroidal anti-inflammatory drug.

In addition to the medical history, dietary history, and physical examination, a variety of laboratory studies can assist in making the diagnosis of iron deficiency anemia. As noted previously, patients have a microcytic, hypochromic anemia in which the Hb and the red cell indices (MCV) and mean corpuscular Hb concentration (MCHC) are lower than normal for age. A widened RDW in the presence of a low MCV is an excellent screening test for iron deficiency anemia. The RDW index ($\text{MCV}/\text{RBC} \times \text{RDW}$) can differentiate between iron deficiency anemia and thalassemia trait with a high specificity, with an index of at least 220 indicative of iron deficiency [28]. Other such indices have been reported, with their value primarily being the ability to guide clinicians in their choice between empiric iron therapy and obtaining a Hb electrophoresis to confirm thalassemia trait [29]. In severe cases, such as the one presented here, these formulas are less valuable because thalassemia traits rarely cause anemia of this degree.

In cases of iron deficiency anemia, the peripheral smear reveals erythrocytes that are hypochromic and microcytic (Figures 1 and 2). The smear is an invaluable tool in ruling out rare causes of microcytic anemia, such as hereditary pyropoikilocytosis, which lead to the production of bizarre-shaped cells.

The reticulocyte count is usually normal but can be low, reflecting impaired RBC production in the absence of sufficient iron. Patients with severe iron deficiency anemia can have either marked thrombocytosis, or thrombocytopenia. The etiology of changes in platelet count in the setting of anemia continues to be the subject of debate [30-32]. Other markers of iron deficiency include free erythrocyte protoporphyrin, serum ferritin, serum transferrin receptor level, CHr, and iron saturation percentage. Serum ferritin reflects the level of body iron stores and is a sensitive indicator of iron deficiency when the concentration is less than 12 to 15 ng/mL. It should be kept in mind that serum ferritin is normal or elevated in infectious disorders, which has the potential for reducing its value in iron-deficient patients with active

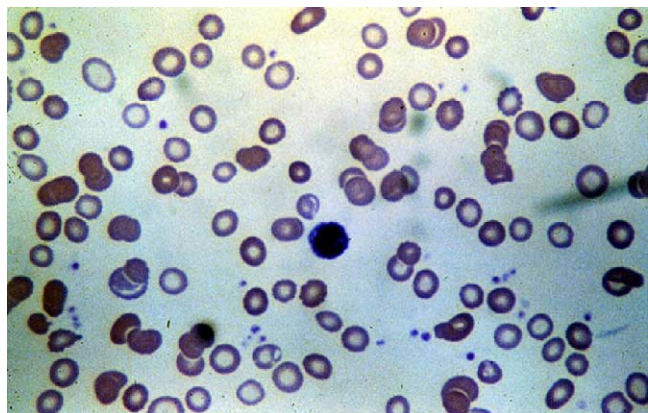


Figure 1 Iron deficiency anemia.

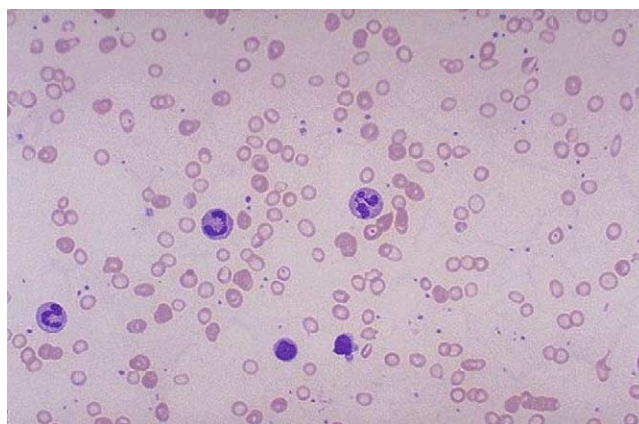


Figure 2 Hypochromic and microcytic erythrocytes in iron deficiency anemia.

infection or inflammation. The serum transferrin receptor level is a sensitive measure of iron deficiency and correlates well with Hb and other parameters of iron status [33]. It is of particular use in distinguishing iron deficiency from anemia of chronic disease [34] as it rises in proportion to tissue iron deficit and is not an acute-phase reactant. Measurement of the serum transferrin receptor has increased sensitivity in differentiating between these 2 conditions when the serum ferritin is measured simultaneously, and the ratio of TfR/log ferritin (TfR-F index) is calculated. This ratio is an outstanding parameter for the identification of patients with depleted iron stores [35]. The utility of this test may be limited based on its lack of widespread availability in hospital laboratories.

The differential diagnosis of a microcytic anemia includes lead poisoning, chronic inflammation, copper deficiency, and congenital sideroblastic anemia. However, iron deficiency anemia and thalassemia are the most common causes seen in children. As noted previously, the RDW index can help discriminate between the two. In addition, a Mentzer index (MCV/RBC ratio) of at least 13 indicates iron deficiency anemia, whereas a ratio less than 13 indicates thalassemia trait with a relatively high (82%) specificity [36].

Treatment involves supportive care for patients who are profoundly symptomatic of their anemia, followed by iron replacement. Oral iron corrects iron deficiency in almost all patients and is well tolerated with a much lower incidence of side effects than parenteral iron dextran therapy. The usual dose ranges from 3 to 6 mg/kg per day of elemental iron in divided doses. Patients typically show a prompt reticulocytosis within 5 to 7 days, followed by an increase in Hb by 1 to 2 g/wk until normal levels are achieved, typically within 4 to 6 weeks of initiating therapy. Treatment should be continued an additional 2 to 3 months to replenish iron stores. In patients such as the one presented here, restriction of milk

intake to no more than 24 oz/d is essential to prevent further iron deficiency [37]. Red blood cell transfusion is rarely necessary in iron deficiency anemia, even in severe cases, owing to the brisk erythropoietic response seen with iron supplementation. However, children with cardiac or pulmonary comorbidities may require transfusion support to avoid life-threatening cardiorespiratory distress. In these cases, careful attention to hemodynamic parameters and fluid status combined with slower infusion rates is particularly important [38].

Case Presentation 2

An 8-year-old girl presents to the ED with a 6-day history of fever to 104.3°F, malaise, and pallor. Her parents indicated that she had been well before this illness, but that in the past day she had a markedly decreased appetite and reduced activity. There was no significant past medical history noted and the patient was not taking any medications other than acetaminophen for fever. Her birth history included a term delivery with no complications. She has been growing well and met all developmental milestones. Before the onset of illness she had been attending school regularly, and her parents were unaware of any large outbreaks of illness. Her family history revealed no significant medical illnesses. She lived with both parents and her 4-year-old brother who was noted to be well. In addition to the aforementioned history, the parents were asked about epistaxis, bleeding from the gums, hematuria, hematochezia, changes in the color or quality of the urine, the presence of any abdominal pain, rashes, bruising or petechiae, joint pain, history of childhood illnesses and immunizations, and family history of any significant illness, all of which were negative.

Physical examination was significant for a tired-appearing child who was markedly pale, including pallor of the mucous membranes and nail beds. Her neck was supple with shotty anterior cervical lymphadenopathy. The oropharynx and tonsils were unremarkable. The cardiac examination revealed a soft systolic ejection murmur. The lungs were clear to auscultation with no adventitious sounds. Examination of the abdomen revealed mild hepatosplenomegaly but no pain to palpation. There was no inguinal lymphadenopathy noted. The skin was pale but warm. There were no petechiae, purpura, or ecchymoses noted. The capillary refill was less than 3 seconds.

The initial CBC revealed a marked normocytic anemia with a Hb concentration of 4.9 g/dL and a MCV of 75 fL. The WBC was $6.0 \times 10^9/L$ with a normal differential, and a platelet count of $169 \times 10^9/L$. The reticulocyte count was 0.9%. Serum chemistries, including liver function tests and uric acid, were normal. A serum indirect bilirubin concentration was slightly elevated at 1.3 mg/dL. A direct Coombs test was performed and found to be negative. A peripheral blood smear revealed poikilocytosis

and macrocytosis with occasional spherocytes and nucleated RBCs.

The findings of hepatosplenomegaly, severe anemia with unusual erythrocyte morphology, and mild thrombocytopenia prompted an evaluation by a hematologist and a bone marrow biopsy and aspirate. Evaluation of the bone marrow showed a marked absence of maturing erythroid precursor cells and the presence of giant pronormoblasts with an adequate number of myeloid precursors and megakaryocytes. With the presence of giant pronormoblasts, the patient was felt to have a transient aplastic crisis secondary to parvovirus B19 infection. Viral titers were sent and the patient was transfused with packed RBCs with relief of the symptoms of her anemia. After the confirmation of parvovirus B19 infection, she was followed by her pediatrician and recovered without any sequelae.

Case Discussion

The differential diagnosis for normocytic anemia with reticulocytopenia in this 8-year-old girl with a history of fever and malaise includes acute blood loss, early iron deficiency, connective tissues disorders, liver disease, malignancy (including bone marrow infiltration), aplastic anemia, transient aplastic crisis, and dyserythropoietic anemia. The medical history and physical examination of this patient can help rule out hemorrhage, connective tissue disorders, and liver disease. Given that the count was normal without peripheral blasts, and that the platelets were normal albeit at the lower end of the reference range, anemia secondary to bone marrow infiltration appears less likely. Early iron deficiency, although possible, would not explain the patient's fevers and malaise. Congenital dyserythroblastic anemias are a group of poorly understood hereditary disorders of erythropoiesis characterized by ineffective red cell production and abnormal nuclei within the erythroid progenitor cells [39]. Congenital dyserythroblastic anemia can present at anytime between birth and adulthood. Patients often have a moderate hemolytic anemia, abnormal erythrocyte morphology, and reticulocytopenia relative to the degree of anemia. Evaluation of the peripheral smear and bone marrow are essential for diagnosis.

More commonly, acute failure of erythropoiesis may follow various viral infections, including cytomegalovirus, Epstein-Barr virus, HIV, and, as this case illustrates, parvovirus B19, which is the best-documented viral cause of a transient aplastic crisis characterized by a normocytic anemia. Parvovirus B19 is a small, single-stranded DNA virus that is the cause of erythema infectiosum (fifth disease) in children. Fever and nonspecific influenza-like symptoms can occur early, during the viremic phase, followed by facial erythema, a reticulated erythematous rash on the trunk, and occasionally by joint pains or arthritis that can occur up to 2 weeks after initial

infection, corresponding to the appearance of antiviral antibodies. It should be noted that some patients might have asymptomatic infection [40]. Typically, serologic testing after the appearance of cutaneous symptoms shows seroconversion by the presence of immunoglobulin (Ig) M antibodies or the new presence of IgG antibodies in those patients previously exposed.

Parvovirus B19 is capable of causing a transient red cell aplasia in patients with or without an underlying hematologic disorder. The only known natural host cell of parvovirus B19 is the human erythroid progenitor [41] where it binds to the erythrocyte P antigen (globoside) and exerts a cytotoxic effect. Characteristic nuclear inclusions can be seen in erythroblasts on evaluation of the bone marrow, and the presence of giant pronormoblasts are pathognomonic for parvovirus infection (Figure 3). Hemophagocytosis can also be seen in the bone marrow and may account for the occasional leukopenia and thrombocytopenia seen with these infections [42]. The peripheral smear shows a lack of polychromasia indicating decreased erythropoiesis in the face of anemia (Figure 4).

The transient aplasia from parvovirus infection should not be confused with transient erythroblastopenia of childhood (TEC), which is a severe transient hypoplastic anemia occurring mainly in healthy children between the ages of 6 months and 3 years. In these cases, anemia develops slowly and may last for as long as 1 to 2 months. Parvovirus and human herpesvirus 6 have been proposed as causes of TEC, but currently there is no proof for any single agent causing TEC [43].

In patients with increased destruction of erythrocytes, or a high demand for the production of RBCs, such as those with sickle cell anemia, hereditary spherocytosis, or red cell enzyme defects, acute parvovirus infection can cause an abrupt cessation of erythropoiesis that results in a profound anemia [42]. This transient aplastic crisis is typically associated with the viremic phase of parvovirus infection, with a return of erythropoiesis after the production of antiviral antibodies. Because infection with

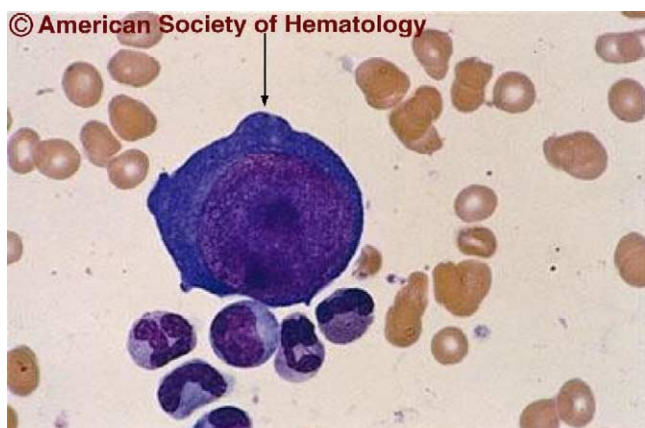


Figure 3 Giant pronormoblast typical for parvovirus B19.

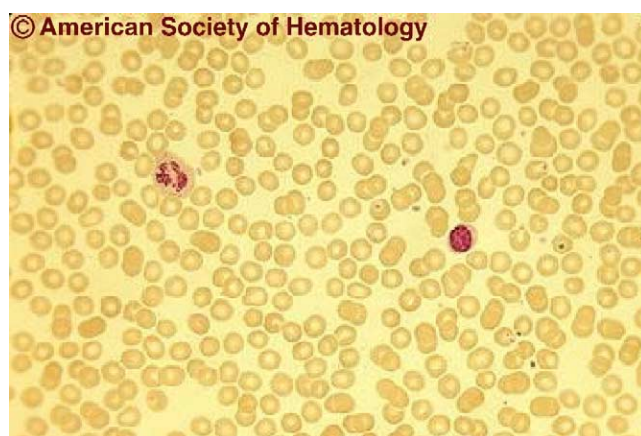


Figure 4 Parvovirus B19–induced pure red cell aplasia.

the virus is usually transient, with recovery occurring within 2 weeks, anemia is typically not present or not noticed in otherwise normal children. Thus, the presence of a severe anemia in a patient with parvovirus B19 infection who is not known to have an underlying hematologic disorder should prompt a more thorough evaluation and a referral to a pediatric hematologist for further evaluation.

Recovery from parvovirus B19 infection is spontaneous, typically heralded by a wave of nucleated RBCs and reticulocytosis in the peripheral smear. Transfusion with packed RBCs may be necessary, as it was in this case, for symptomatic anemia. Rarely, patients may have persistent parvovirus infection, which may indicate an inability to mount an adequate antibody response and should lead to further investigation. Chronically infected patients may require treatment with intravenous immune globulin, which contains a neutralizing antibody to parvovirus B19 [44]. The presence of persistent parvovirus infection requires examination of the bone marrow by polymerase chain reaction in the absence of specific antibodies [45].

Case Presentation 3

A 4-year-old girl who was previously in good health presented to the ED when she was noted by her mother to have intermittent tactile fever for 3 to 4 days, followed by 2 days of increasing pallor and progressive jaundice. In addition, the patient's mother also noted her to have increased fatigue and decreased appetite. She had one episode of emesis that was not bloody and normal bowel movements. There was no complaint of abdominal pain, joint swelling, rash, or headache. Her parents were particularly concerned because of a change in the color of her urine, which they noted to be dark yellow. The past medical history was noncontributory and the family history was negative for any hematologic disorders, autoimmune disorders, or bleeding diatheses. The patient took no medications except for acetaminophen for her fever.

Physical examination revealed an alert and playful child. Her vital signs included a temperature of 37.6°C, heart rate of 142 beats per minute, respiratory rate of 28 per minute, and a blood pressure of 119/69 mm Hg. A significant finding on the physical examination was scleral icterus. Examination of the oropharynx showed no tonsillar enlargement. The neck was supple with no lymphadenopathy. The lungs were clear to auscultation with no adventitious sounds. The cardiac examination revealed tachycardia with a grade II/VI flow murmur but no third or fourth heart sounds. The extremities were well perfused with brisk capillary refill. The abdominal examination demonstrated no hepatomegaly but the spleen tip could be appreciated at the left costal margin. The skin was warm but sallow.

The initial CBC showed a WBC of 16200 with an absolute neutrophil count of 10600. The Hb was 5.1 g/dL and the hematocrit was 12.9%. The platelets were within normal limits at 427000. Examination of the peripheral blood smear showed 3+ spherocytes, polychromasia, and slight rouleaux formation. The reticulocyte count was 3.2%. Liver function tests and serum chemistries were normal with the exception of an indirect bilirubin elevated at 3.5 mg/dL.

The patient's symptoms, physical examination, and laboratory studies indicated a hemolytic anemia. The differential diagnosis included congenital hemolytic anemias secondary to disorders of the red cell membrane, hemoglobinopathies, or red cell enzyme defects. The absence of a family history of anemia, splenomegaly, jaundice, or gallstones made these possibilities less likely. The other diagnostic possibilities were primarily-acquired hemolytic anemias, including those secondary to drugs or toxins, or the mechanical destruction of RBCs due to microangiopathy. The lack of a significant antecedent illness, medication use, or toxin exposure made these possibilities unlikely. The remaining diagnostic possibility was an antibody-mediated hemolytic anemia, which could be either idiopathic, or secondary to a more generalized autoimmune process, or after exposure to a drug.

A direct Coombs test was weakly positive for complement but negative for IgG. Based on the laboratory findings, and the clinical history, including the antecedent exposure to the cold, a diagnosis of paroxysmal cold hemoglobinuria (PCH) was considered by the consultant. As such, the patient had a Donath-Landsteiner antibody test performed in the special hematology lab [46]. In this test, 3 mixtures were prepared. The patient's serum was mixed with control cells positive for P-antigen. The patient's serum was mixed with control serum and control cells positive for P-antigen. The third mixture was composed of control serum and P-antigen-positive cells. Each of these 3 mixtures was incubated for 3 different phases, a warm phase (37°C for ninety minutes), a cold phase (melting ice for 90 minutes), and a biphasic reaction (melting ice for

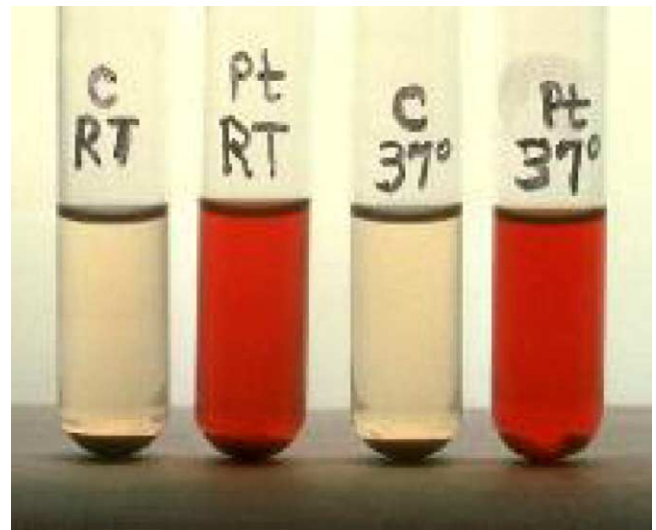


Figure 5 Donath-Landsteiner antibody test for PNH.

30 minutes and then 37°C for 60 minutes). The result of this test showed that the first mixture (patient's serum and P-positive cells) had hemolysis in the biphasic reaction with no hemolysis in either the isolated cold or the warm phase. In contrast, mixing the patient's serum with a control serum abrogated hemolysis in either the cold or the warm phase (Figure 5). These findings demonstrated the existence of biphasic autoantibodies to RBC P-antigen that appear at low temperatures but not at constant warm temperatures, establishing the diagnosis of PCH.

The patient was admitted to the hospital from the ED and started on high-dose corticosteroids (dexamethasone, 1 mg/kg every 6 hours) and transfused with 15 mL/kg of ABO compatible cross-matched blood in 5 mL/kg aliquots. Once the diagnosis had been established and the patient's Hb was noted to be stable, she was discharged on a prolonged steroid taper. Importantly, her parents were instructed to keep her warm and avoid exposure of her extremities to the cold.

Case Discussion

One of the most serious causes of severe anemia in pediatrics is autoimmune hemolytic anemia (AIHA), an antibody-mediated disorder that occurs most commonly in young children. In the AIHAs, the patient's antibodies are directed against antigens on the patient's own RBCs. Antibody-coated erythrocytes are destroyed because of intravascular hemolysis or are removed prematurely from the circulation by the reticuloendothelial system. Autoimmune hemolytic anemia can be broadly classified as either primary or secondary. Primary AIHA is typically idiopathic and includes lysis of erythrocytes due to the production of either warm autoantibodies that typically bind to the Rh antigens, or cold autoantibodies that usually bind to the I/i antigens. Warm antibodies usually

consist of IgG molecules that optimally bind at 37°C and rarely fix complement. Cold antibodies, on the other hand, consist of IgM molecules that optimally bind at 4°C and usually fix complement. Also included in the category of primary AIHA is paroxysmal cold hemoglobinuria, in which an IgG autoantibody binds to RBCs at cold temperatures and fixes complement leading to cell lysis at warm temperatures. Secondary AIHA includes hemolysis secondary to infection, malignancy, or exposure to certain drugs or chemicals (ie, quinine, aspirin, chlorpromazine, antibiotics, naphthalene). Secondary AIHA also occurs as a consequence of systemic autoimmune diseases such as systemic lupus erythematosus, scleroderma, and rheumatoid arthritis.

Autoimmune hemolytic anemia may occur suddenly or may follow an indolent course. Acute manifestations typically include the triad of pallor, jaundice, and dark urine. The degree of hemolysis can be profound, with Hb levels falling as low as 1 to 2 g/dL at the time of diagnosis, leading to symptoms of pallor, scleral icterus, fatigue, exercise intolerance, and tachycardia. Hepatosplenomegaly may also be seen in AIHA, especially in warm (IgG) antibody-mediated hemolysis in which coated RBCs are trapped and destroyed in the spleen with subsequent extravascular hemolysis.

As indicated previously, PCH is a hemolytic anemia due to cold-reacting IgG antibodies characterized by the sudden onset of hemoglobinuria after exposure of the patient to the cold. Other symptoms include jaundice, weakness, pallor, and, if the anemia is sufficient, cardiac compromise. The diagnosis is made by the demonstration of a cold-reacting IgG (Donath-Landsteiner antibody) in the serum using the methodology described. Paroxysmal cold hemoglobinuria occurs frequently after a viral illness or inoculation, most frequently in children younger than 5 years. The anemia, as noted, can be severe, but the syndrome resolves over 3 to 6 weeks.

The key to diagnosis of hemolytic anemia is the antiglobulin (Coombs) test [47]. The antiglobulin test was first introduced into clinical practice in 1945 by RR Coombs who showed that it could be used to detect non-agglutinating red cell antibodies (indirect antiglobulin test) or sensitized red cells (direct antiglobulin test, [DAT]). Most non-agglutinating (incomplete) antibodies are IgG, although some antibodies are IgM. It appears that these antibodies do not spontaneously cause agglutination. This is due to a strong electronegative charge on the red cell surface that prevents the cells from coming into close proximity, a requirement for an antibody to cause agglutination. The antiglobulin reagent is able to bridge these negative forces. Current antiglobulin reagent (Coombs reagent) preparations contain a “cocktail” of monoclonal antibodies directed against human IgG and C3. The DAT is used to detect IgG or C3 bound to the surface of the red cell and thus an immune etiology. Nonimmune causes of hemolysis, such as disseminated

intravascular coagulopathy, thrombotic thrombocytopenic purpura, mechanical hemolysis, such as those due to artificial valves or severe burns, hemoglobinopathies (sickle cell, thalassemia), red cell enzyme deficiencies (G6PD, pyruvate kinase), and red cell membrane defects (hereditary spherocytosis, PNH) will have a negative DAT. Immune causes of hemolysis, including AIHAs, drug-induced hemolysis, and delayed or acute hemolytic transfusion reactions, are characterized by a positive DAT. Positive DATs without hemolysis occur in patients with autoimmune diseases such as systemic lupus erythematosus and some infectious diseases (eg, infectious mononucleosis). A small proportion of normal individuals will also have a positive DAT without evidence of decreased red cell survival. Thus, a positive DAT, by itself, does not mean that the patient has an immune hemolytic anemia.

The DAT is a 5- to 10-minute laboratory procedure performed by incubating RBCs with the antiglobulin reagent. A positive DAT due to IgG is seen most frequently in patients with warm autoantibodies. Approximately half of these patients also have C3 on the red cell membrane. IgG bound to the red cell surface can be eluted and its specificity determined. A positive DAT due to complement (C3) alone is seen in patients with cold autoantibodies, PCH, and in some drug-induced hemolytic anemias. The offending antibodies are typically of the IgM isotype and efficiently bind complement. IgM antibodies are not directly detected by the DAT, but are detected indirectly by the presence of C3 on the red cell surface. Cold AIHAs may be associated with intravascular hemolysis due to complement-mediated lysis. Extravascular removal of C3-coated cells can occur via complement receptors on phagocytes in the liver.

Treatment of AIHA as well as the prognosis is predicated on the underlying diagnosis and involves the diminution of the concentration of antibody, a reduction in its effectiveness in mediating erythrocyte lysis, or both. Management of patients with AIHA should be done in coordination with a pediatric hematologist. Transfusion is frequently required in patients with symptoms related to the anemia, or in those whom the Hb concentration is falling rapidly [48]. However, transfusion may offer only transient benefit because of the presence of autoantibodies. In these cases, transfusion therapy should be discussed in detail with the blood bank staff to ensure that the “most compatible” blood is used. Corticosteroids (eg, prednisone 2-4 mg/kg per day) may be beneficial, especially in patients with IgG-mediated (warm antibody) hemolytic anemia. A response is usually seen within 24 to 48 hours and should be continued until the hemolysis decreases, after which the dose can be slowly tapered over several months. During this time, Hb concentration, reticulocyte count, and the intensity of the Coombs test should be followed closely. Patients who do not respond to corticosteroid therapy may benefit from other therapeutic modalities, including cytotoxic agents, immunosuppressive

Table 7 Physical findings associated with anemia.

| Organ System | Physical Finding | Associated Diseases |
|--------------|-----------------------------------|---|
| Skin | Hyperpigmentation | Fanconi anemia, dyskeratosis congenital |
| | Vitiligo | Vitamin B ₁₂ deficiency |
| | Jaundice Petechiae, purpura | Hemolysis Bone marrow infiltration, autoimmune hemolysis with autoimmune thrombocytopenia (Evan syndrome) |
| | Reticulated rash | Parvovirus, EBV |
| | Malar rash | SLE autoantibodies (hemolytic anemia) |
| Head | Frontal bossing | Thalassemia major, severe iron deficiency |
| Eyes | Microcephaly | Fanconi anemia |
| | Blue sclera | Iron deficiency |
| | Kayser-Fleisher ring | Wilson disease |
| Mouth | Glossitis | B ₁₂ or iron deficiency |
| | Angular stomatitis | Iron deficiency |
| | Cleft lip | Diamond-Blackfan anemia |
| Chest | Shield chest | Diamond-Blackfan anemia |
| | Murmur | Endocarditis, prosthetic heart valve, severe anemia |
| Abdomen | Hepatomegaly | Hemolysis, chronic disease, hemangioma, cholecystitis (hemolytic anemia, hemoglobinopathy, RBC membrane defect), infiltrative tumor |
| | Splenomegaly | Hemolysis, thalassemia, malaria, lymphoma, EBV |
| Extremities | Absent thumbs | Fanconi anemia |
| | Triphalangeal thumb | Diamond-Blackfan anemia |
| | Spoon nails | Iron deficiency |
| | Beau line (nails) | Heavy metal toxicity |
| | Mees line (nails) | Heavy metal toxicity, sickle cell anemia |
| | Dystrophic nails | Dyskeratosis congenital |
| | Edema | Milk-induced protein-losing enteropathy with iron deficiency |

Table 7 continued

| Organ System | Physical Finding | Associated Diseases |
|--------------|-----------------------|---|
| Nerves | Irritable, apathetic | Iron deficiency |
| | Peripheral neuropathy | Vitamin B ₁ , B ₁₂ , or E deficiency, lead toxicity |
| | Dementia | Vitamin B ₁₂ or E deficiency |
| | Ataxia | Vitamin B ₁₂ or E deficiency |
| | Stroke | Sickle cell anemia, profound anemia, paroxysmal nocturnal hemoglobinuria |

EBV indicates Epstein-Barr virus; SLE, systemic lupus erythematosus.

agents, or plasmapheresis[49,50]. Patients refractory to multiple modalities may require splenectomy to affect a durable increase in Hb concentration.

The treatment of PCH is similar to that of AIHAs due to warm-reacting IgG, whereby prednisone is often effective in reducing the amount of antibody. Avoidance of the cold can also be effective in reducing the likelihood of hemolysis. Because the majority of cases of PCH are transient, patients are not expected to have another episode once treatment is complete.

Summary

As previously discussed, anemia may be a primary event, indicating hematologic disease, or it may be a manifestation of a wide variety of diseases. Although all patients presenting to the ED with anemia require a thorough evaluation, patients who appear acutely ill should be closely followed because acute blood loss, acute hemolysis, or splenic sequestration of erythrocytes may require prompt treatment. The physical examination of the patient with anemia may lead to important diagnostic clues (Table 7). Of note, findings of abnormal vital signs, weight loss or failure to thrive, shortness of breath or fatigue, generalized adenopathy, edema, ecchymoses or petechiae, or organomegaly should lead the examiner to suspect that a potentially serious underlying disorder is present. Similarly, findings of neutropenia and/or thrombocytopenia, a high MCV with a normal RDW, or blasts in the peripheral smear should prompt the ED clinician to consult with a hematologist.

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