Causes of Anemia Due to Diminished Red Blood Cell Production in Pediatrics

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ABSTRACT

The critical feature that distinguishes the anemias discussed in this article is the presence of an inappropriately low reticulocyte count for the degree of anemia. This is consistent with nutritional deficiencies, decreased erythropoietin levels, aplastic anemia, or inherited bone marrow failure syndromes. In addition, bone marrow replacement by a benign or malignant process, including those associated with ineffective erythropoiesis (eg, congenital dyserythropoietic anemias), comprise the differential diagnosis. Anemia causes increased morbidity and mortality in pediatric population; the absolute reticulocyte count (ARC) can be calculated by multiplying the percent reticulocytes by the RBC count/L. In a patient with anemia, ARC values within the "normal range" (generally $50-100 \times 10^9/L$) indicate an inappropriate response and suggest that there is an underlying red cell production issue due to intrinsic or extrinsic factors, or a combination of the two. The mean corpuscular volume (MCV) is another valuable red cell index that narrows the differential diagnosis of anemia due to diminished production. It is critical, however, to check age-specific normal values for MCV and to recognize that certain diseases can present with low, normal, and/or high MCVs. Finally, the red cell distribution width (RDW) assists in differentiating whether the anemia is likely due to a mixed process (wide RDW) or from a single cause (normal RDW). However, the management of anemia depends on the etiology. Early diagnosis and prompt treatment improve the quality of life of patients.

Keywords: anemia; red blood cell production; pediatrics

INTRODUCTION

Anemia is defined as a hemoglobin concentration or hematocrit less than normal for a specific age and gender. Both age and gender are essential considerations when making a diagnosis of anemia, as is the fact that some laboratories use only adult normal range values and will erroneously report abnormal pediatric levels of hemoglobin as normal. Using a definition of anemia as 2 standard deviations below the mean results in 2.5% of children meeting the criteria for anemia. Children with such "statistical anemia" should continue to follow along the same hembogloin percentile for age over time; but must also be confirmed as healthy and "normal" by ruling out other etiologies for anemia. Age-related normal means and ranges for hemoglobin, hematocrit, and mean corpuscular volume (MCV) are shown elsewhere.

The production of mature red blood cells (RBCs) from hematopoietic stem cells is a tightly regulated process that is dependent on growth factors, specific niches, and physiologic needs.[1] Erythropoiesis normally proceeds at a basal rate, allowing for the replacement of senescent RBCs, which constitute 1% of red cell mass, with young reticulocytes produced within the bone marrow.

However, red cell production can be enhanced by as much as 10- to 20-fold in a variety of clinical settings in which there is decreased arterial blood oxygenation and/or oxygen delivery to the tissues. In the absence of critical components required for erythropoiesis, the bone marrow is unable to produce an adequate number of red cells, ultimately leading to anemia. Anemia may be the first hematologic finding in a child with abnormal bone marrow function; it may be the sole problem (single cytopenia) or occur in conjunction with deficits in other cell lineages (pancytopenia). The cause may be a deficiency of a required nutrient (eg, iron, folic acid, vitamin B12), the inability of the marrow to use nutrients because of concomitant medical conditions (eg, inflammation, hypothyroidism), or intrinsic bone marrow failure. Bone marrow failure may be either inherited or acquired (aplastic anemia). This article will highlight the causes of anemia that are due to diminished RBC production in pediatrics.

Mechanisms of anemia
- Decreased production of RBCs (hypoproliferation).
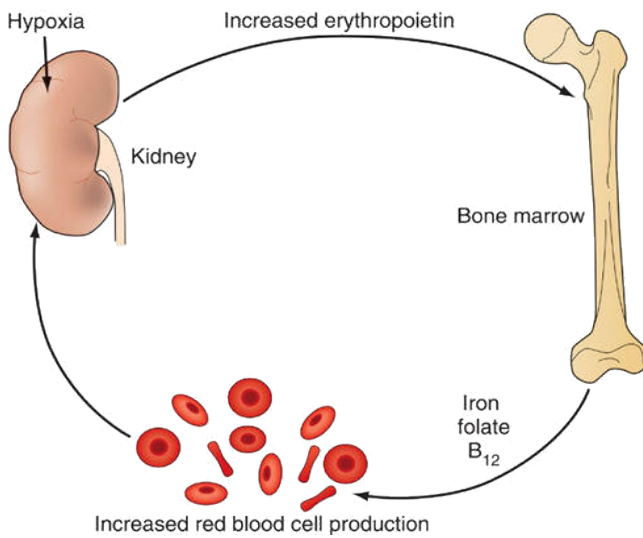- Increased destruction of RBCs (hemolysis).
- Acute blood loss (hemorrhage).

FIGURE 1: Normal erythropoiesis[2]

FIGURE 2: Normal mean and lower limits of normal for hemoglobin, hematocrit, and mean corpuscular volume[3]

CLINICAL MANIFESTATIONS

Common symptoms of anemia include pallor, irritability, fatigue, and lightheadedness. Children, especially young children, may tolerate severe anemia (hemoglobin <5 g/dL) quite well, especially if it is chronic with minimal to no symptoms. [1] In severe or acute anemia, tachycardia is present. On physical exam, the most notable finding of anemia is skin pallor that may be subtle and apparent only in severe or acute cases. Pale mucous membranes and conjunctivae as well as pallor within the palmar creases may also be present. Children with iron deficiency anemia may also have pica, the compulsion to eat nonfood substances such as dirt, clay, paper, laundry starch, or ice. Jaundice, best appreciated as yellow sclerae, suggests a hemolytic process, although some children with chronic hemolytic anemias may not have overt scleral icterus. Patients with red cell membrane defects such as hereditary spherocytosis or enzymopathies such as pyruvate kinase deficiency should have careful assessment for splenomegaly. Lymphadenopathy, hepatomegaly, rashes, and rheumatologic conditions such as arthritis should be assessed to rule out malignancy or other systemic diseases.[4]

NORMAL RETICULOCYTE COUNT

The reticulocyte count reflects the rate at which new erythrocytes are being produced and released from the bone marrow.

Reticulocytes contain stainable reticulum for about 1 to 2 days, so the normal reticulocyte count is 1.0% to 2.0%. Normal absolute reticulocyte count (ARC) varies by laboratory method used, but generally is 50 to 100 × 109/L. Low ARC values (< 50 × 109/L) indicate erythroid underproduction, and increased values (> 100 × 109/L) suggest erythroid marrow hyperplasia, often associated with hemolysis.[5] Transiently high reticulocyte counts may also be present after acute blood loss, recovery from transient erythoblastopenia of childhood, and institution of therapy for nutritional deficiencies such as iron, folic acid, or vitamin B12. Reticulocytosis can be recognized by polychromasia on the blood smear and may be accompanied by an elevated MCV because reticulocytes are larger than mature RBCs.[6] An accurate reticulocyte count is key to the initial classification of anemia. Reticulocytes are red cells that have been recently released from the bone marrow. They are identified by staining with a supravital dye that precipitates the ribosomal RNA. These precipitates appear as blue or black punctate spots and can be counted manually or, currently, by fluorescent emission of dyes that bind to RNA. This residual RNA is metabolized over the first 24-36h of the reticulocyte's life span in circulation. Normally, the reticulocyte count ranges from 1 to 2% and reflects the daily replacement of 0.8-1.0% of the circulating red cell population. A corrected reticulocyte percentage or the absolute number of reticulocytes provides a reliable measure of effective red cell production.
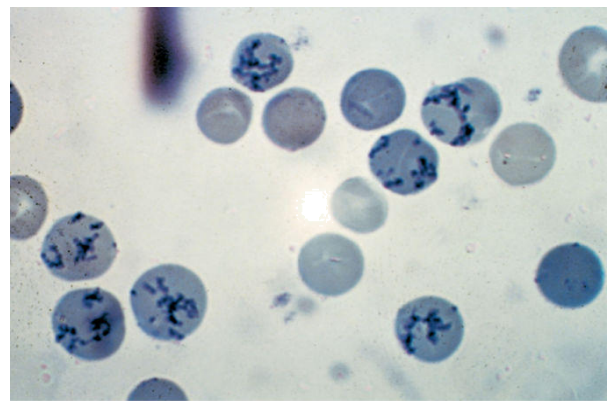

FIGURE 3: Reticulocytes: Methylene blue stain demonstrates residual RNA in newly made red cells[7]

In the initial classification of anemia, the patient's reticulocyte count is compared with the expected reticulocyte response.[7] In general, if the EPO and erythroid marrow responses to moderate anemia [hemoglobin <100 g/L (10 g/dL)] are intact, the red cell production rate increases to two to three times normal within 10 days following the onset of anemia. In the face of established anemia, a reticulocyte response less than two to three times normally indicates an inadequate marrow response. To use the reticulocyte count to estimate marrow response, two corrections are necessary. The first correction adjusts the reticulocyte count based on the reduced number of circulating red cells. With anemia, the percentage of reticulocytes may be increased while the absolute number is unchanged. To correct for this effect, the reticulocyte percentage is multiplied by the ratio of the patient's hemoglobin or hematocrit to the expected hemoglobin/hematocrit for the age and sex of the patient.

Correction #1 for Anemia:

This correction produces the corrected reticulocyte count.

In a person whose reticulocyte count is 9%, hemoglobin 7.5 g/dL, and hematocrit 23%, the absolute reticulocyte count = 9 × (7.5/15) [or × (23/45)] = 4.5%

Note. This correction is not done if the reticulocyte count is reported in absolute numbers (e.g., 50,000/µL of blood)

Correction #2 for Longer Life of Prematurely Released Reticulocytes in the Blood:

This correction produces the reticulocyte production index.

In a person whose reticulocyte count is 9%, hemoglobin 7.5 gm/dL, and hematocrit 23%, the reticulocyte production index

$$= 9 \times \frac{(7.5/15)(\text{hemoglobin correction})}{2(\text{maturation time correction})} = 2.25$$

FIGURE 4: Calculation of reticulocyte production index.

This provides an estimate of the reticulocyte count corrected for anemia. To convert the corrected reticulocyte count to an index of marrow production, a further correction is required, depending on whether some of the reticulocytes in circulation have been released from the marrow prematurely. For this second correction, the peripheral blood smear is examined to see if there are polychromatophilic macrocytes present. These cells, representing prematurely released reticulocytes, are referred to as "shift" cells. The correction is necessary because these prematurely released cells survive as reticulocytes in circulation for >1 day, thereby providing a falsely high estimate of daily red cell production. If polychromasia is increased, the reticulocyte count, already corrected for anemia, should be corrected again by 2 to account for the prolonged reticulocyte maturation time.

The second correction factor varies from 1 to 3 depending on the severity of anemia.[8] In general, a correction of 2 is simply used. If polychromatophilic cells are not seen on the blood smear, the second correction is not indicated. The now doubly corrected reticulocyte count is the reticulocyte production index, and it provides an estimate of marrow production relative to normal. In many hospital laboratories, the reticulocyte count is reported not only as a percentage but also in absolute numbers. If so, no correction for dilution is required. A summary of the appropriate marrow response to varying degrees of anemia is shown below.
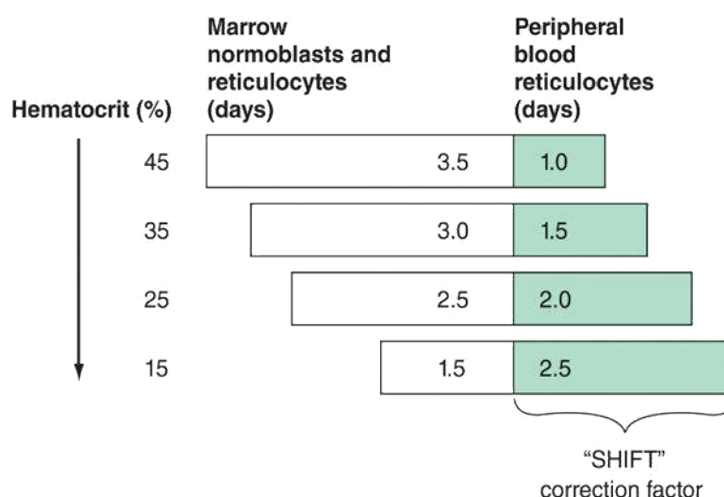
Hematocrit (%)	Marrow normoblasts and reticulocytes (days)	Peripheral blood reticulocytes (days)
45	3.5	1.0
35	3.0	1.5
25	2.5	2.0
15	1.5	2.5

"SHIFT" correction factor

FIGURE 5: Correction of The Reticulocyte Count

To use the reticulocyte count as an indicator of effective red cell production, the reticulocyte number must be corrected based on the level of anemia and the circulating life span of the reticulocytes. Erythroid cells take 4-5 days to mature. At a normal hemoglobin, reticulocytes are released to the circulation with 1 day left as reticulocytes.

However, with different levels of anemia, reticulocytes (and even earlier erythroid cells) may be released from the marrow prematurely. Most patients come to clinical attention with hematocrits in the mid-20s, and thus a correction factor of 2 is commonly used because the observed reticulocytes will live for 2 days in the face of established anemia, a defect in erythroid marrow proliferation or maturation must be present.

HYPOPROLIFERATIVE ANEMIA

MICROCYTIC ANEMIAS WITH INAPPROPRIATELY LOW RETICULOCYTE COUNTS
In pediatrics, the most common nutritional anemia is due to iron deficiency. Anemia may also develop from lead toxicity, which causes impaired synthesis of heme, hemolysis, and shortened red cell survival. Lead toxicity may also be seen in combination with other nutritional deficiencies that lead to anemia. Both iron deficiency anemia and lead toxicity are diagnosed with routine laboratory studies. Rare causes of anemia with an inappropriately low reticulocyte count include the porphyrias, in which there are defects in the synthesis of heme, as well as the sideroblastic anemias, in which there are defects involving the incorporation of iron into the heme molecule.[10]
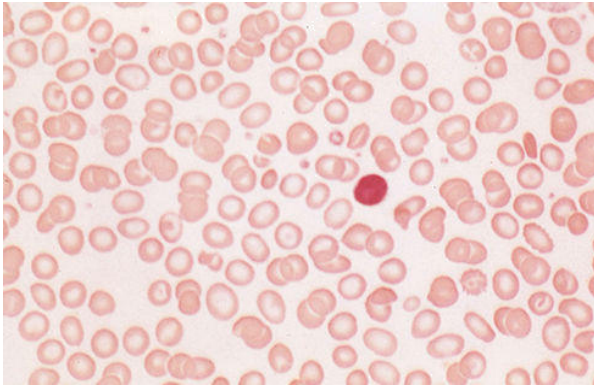

FIGURE 6: Iron-deficiency Anemia

Treatment of iron deficiency should always be coupled with the identification and correction of an underlying cause, if possible. Oral iron is relatively inexpensive and generally sufficient to correct anemia and replenish iron stores.

For lead toxicity, treat with edetate disodium (EDTA) chelation. However, medical evaluation, repeated testing, nutritional intervention to increase iron and calcium intake and decrease fat consumption, treatment of iron deficiency anemia, and investigation of the source of lead exposure are indicated.

NORMOCYTIC ANEMIAS WITH INAPPROPRIATELY LOW RETICULOCYTE COUNTS
Transient aplastic crises in patients with chronic hemolytic anemias (eg, sickle cell disease or thalassemia), chronic parvovirus infection in immunocompromised patients, viral/bacterial suppression of the bone marrow, and adverse effects of certain medications on the bone marrow may result in normocytic anemias with inappropriately low reticulocyte counts.

i. Inflammation or Chronic Disease
Anemia of inflammation or chronic disease is generally normocytic, but when severe may be microcytic. The anemia is usually mild (hemoglobin concentration 8-10 g/dL). Iron studies can help distinguish between anemia of chronic disease (ACD) and iron deficiency anemia.[10] The cause of the anemia is multifactorial and includes both a shortening of RBC survival and a reduction of RBC production. This hypoproliferative state is likely due to elevated hepcidin levels (making iron unavailable for normal erythropoiesis) and inappropriately low erythropoietin levels. Control of the underlying disease or inflammation generally results in improvement of the anemia.
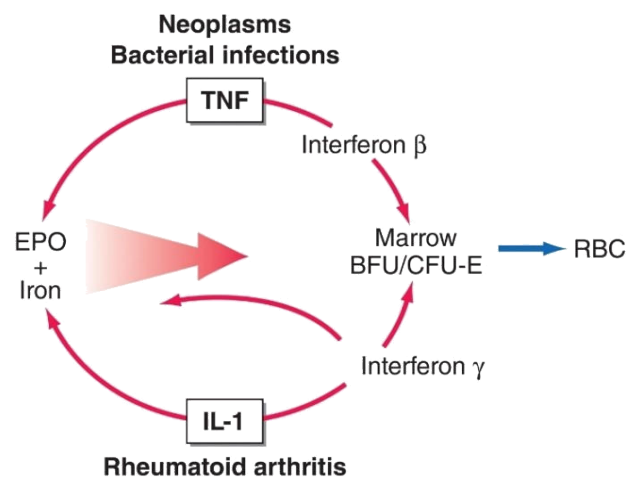

FIGURE 6: Suppression of erythropoiesis by inflammatory cytokines. Through the release of tumor necrosis factor (TNF) and interferon β (IFN-β), neoplasms and bacterial infections suppress erythropoietin (EPO) production and the proliferation of erythroid progenitors (erythroid burst-forming units and erythroid colony-forming units [BFU/CFU-E]). The mediators in patients with vasculitis and rheumatoid arthritis include interleukin 1 (IL-1) and IFN-γ. The red arrows indicate sites of inflammatory cytokine inhibitory effects. RBC, red blood cell.

ii. Hypothyroidism
Some patients with undiagnosed or inadequately treated hypothyroidism may develop marked anemia and even mild pancytopenia. The anemia is normocytic and later macrocytic. Adequate replacement of thyroid hormone should correct the hematologic defects within several months.

iii. Chronic Kidney Disease
Most patients with chronic renal failure develop a normocytic anemia due primarily to a deficiency of erythropoietin. Chronic treatment with recombinant human erythropoietin and iron therapy are often used to maintain a hemoglobin level between 11 and 12 g/dL in these patients.

iv. Malnutrition or Starvation
Patients with malnutrition or anorexia nervosa may have a normocytic, normochromic anemia with acanthocytes, neutropenia, and thrombocytopenia. Blood counts may require several months to recover after adequate caloric intake is restored.

v. Myelophthisic Anemia
Myelophthisic disease occurs when the bone marrow is invaded by tumor cells or granulomas, or if the marrow cavity is destroyed by diseases such as myelofibrosis or osteopetrosis.[10] The bone marrow cavity is gradually occluded by the dense bone, and extramedullary hematopoiesis occurs, resulting in an enlarged spleen and liver.

vi. Transient Erythroblastopenia of Childhood
Transient erythroblastopenia of childhood (TEC) is the spontaneous cessation of erythropoiesis in otherwise healthy children. It is critical to distinguish TEC from Diamond-Blackfan anemia (see below). Transient erythroblastopenia of childhood usually presents in children between ages 6 months and 3 years and persists for weeks to several months. Although the RBC lineage is always involved, neutropenia and thrombocytopenia also may occur but rarely. Transient erythroblastopenia of childhood is a diagnosis of exclusion and can only be confirmed after the fact, when normal erythropoiesis is spontaneously restored.

Bone marrow examination is usually not required, but when performed shows a paucity of erythroid precursors with no other abnormalities. Although there may be some seasonal variation and clustering of cases, there is no clear association with any specific viral infection, and the cause of TEC remains unknown.[11] Management is supportive with RBC transfusion as needed; hemoglobin and reticulocyte counts should be monitored until normal. Once normal hematopoiesis is restored, the disorder does not usually recur and no specific follow-up is needed.

vii. Acquired Idiopathic Aplastic Anemia

Aplastic anemia is usually insidious in onset. The reported incidence is estimated to be 2 per million children per year. There are no unequivocal incidence peaks in childhood, although half of all cases occur in the first 3 decades of life, with no clear race or gender predispositions. Although aplastic anemia is classically associated with exposure to radiation or toxic agents (benzene, pesticides, or medications such as chloramphenicol), it typically results from a combination of exposures, a diversity of host genetic susceptibility factors, and individual differences in the immune response. Patients typically present with fatigue, pallor, and symptomatic thrombocytopenia (epistaxis or bruising). Organomegaly and adenopathy, as well as systemic infection, are rarely present. Evaluation should include questioning about recent illnesses, medications, and exposures; a detailed family history; a thorough physical exam; and basic laboratory testing. A bone marrow biopsy is ultimately required for diagnosis, as the disease is categorized by the degree of peripheral blood cytopenia and bone marrow cellularity.[11] The diagnosis of aplastic anemia requires a bone marrow cellularity less than 25% and 2 of the following: an absolute neutrophil count (ANC) less than 500/μL, a platelet count less than 20,000/μL, and an absolute reticulocyte count (ARC) less than 20,000/μL. Very severe aplastic anemia is characterized by an ANC less than 200/μL. Criteria for mild or moderate aplastic anemia or hypoplastic anemia are not as well established. Such categories are important to guide therapy because patients with severe or very severe aplastic anemia are unlikely to spontaneously recover adequate marrow function. If the diagnosis of aplastic anemia is made, testing for specific viruses including hepatitis A, B, and C; Epstein-Barr virus (EBV); cytomegalovirus (CMV); and parvovirus is suggested. In addition, human leukocyte antigen (HLA) typing of the patient, siblings, and parents is essential for future management of the patient. Although the majority of cases of aplastic anemia are idiopathic, the differential diagnosis includes infectious etiologies as well as the most common IBMFSs. More detailed laboratory testing to exclude a diagnosis of IBMFSs includes cytogenetics with fluorescence in situ hybridization (FISH) from the bone marrow to rule out myelodysplastic syndromes, peripheral blood diepoxybutane (DEB) testing to evaluate for Fanconi anemia, and telomere length to assess for dyskeratosis congenita. In addition, flow cytometry is essential to evaluate for paroxysmal nocturnal hemoglobinuria (PNH), a variable disorder in which the inability to prevent complement-mediated lysis of the RBC leads to intravascular hemolysis and venous thrombosis. The pathophysiology of aplastic anemia varies with the underlying cause. Current studies suggest that in some instances following exposure to a drug, virus, or toxin, aplastic anemia is the result of an immunologic reaction that leads to apoptosis within the bone marrow. In "drug-induced" aplastic anemia, the immune response drug used to treat the infection, rather than the drug itself, may trigger the aplasia. Although aplastic anemia has been reported following both hepatitis A and B, the hepatitis/aplasia syndrome is not usually related to the hepatitis.

In "radiation-induced" aplastic anemia, hypoplasia of the bone marrow suggests that direct toxicity to proliferating cells and supporting stroma is responsible for the aplasia. Treatment of aplastic anemia initially consists of supportive care. Medications and other potentially toxic exposures to the marrow must be avoided, and the patient should be carefully observed pending the results of the diagnostic evaluation. Anemia and thrombocytopenia can be managed with the judicious use of transfusions to minimize the exposure to HLAs that have the potential to decrease the chance of a successful stem cell transplantation (SCT). Standard fever and neutropenia precautions are recommended. Granulocyte colony-stimulating factor (GCSF) has not been shown to have a significant effect in severe aplastic anemia and is therefore not recommended. For children with an HLA-identical sibling donor, immediate SCT offers the best chance of cure, with 5-year survival rates of 80% to 90%. Chronic graft-versus-host disease is encountered less often in children than adults. Graft rejection, which was a significant problem in the early years of SCT, now occurs in less than 5% of cases. For children without an HLA-identical related donor, immunosuppressive therapy using a combination of antithymocyte globulin (ATG) and cyclosporine (which inhibits T-cell proliferation and inhibits transcription of genes for cytokines, including interleukin-2 and γ interferon) plus supportive care results in transfusion independence in 80% to 85% of patients. If immunosuppression does not result in transfusion independence within 3 months, an unrelated stem cell donor source should be sought for a transplant. Overall survival in aplastic anemia, regardless of treatment, has continuously improved over the past decades, probably related to improvements in supportive care and SCT technology.[11]

MACROCYTIC ANEMIAS WITH INAPPROPRIATELY LOW RETICULOCYTE COUNTS

This category of disorders is divided into megaloblastic and nonmegaloblastic conditions. Megaloblastic changes include macroovalocytes, hypersegmented neutrophils, and anisopoikilocytosis on the peripheral blood smear. Also, there is nuclear/cytoplasmic dyssynchrony on bone marrow examination. Macrocytosis without megaloblastic changes is often associated with 1 of the IBMFSs.

Megaloblastic Anemia

i. Folic Acid Deficiency

Folic acid deficiency is rare in some infants and children due to the routine supplementation of commercial infant formulas and flour-containing products such as bread and pasta. Classically, it occurs in severe malnutrition and severe dietary allergies/restrictions, and in infants fed unpasteurized goat's milk. Because folic acid is absorbed in the jejunum, malabsorption may occur due to celiac disease or due to the inhibitory effects of anticonvulsants. Some cytotoxic medications achieve their therapeutic benefit by alteration of folic acid metabolism. Deficiency also may occur in persons with increased folate requirements, such as in chronic hemolytic anemia.[12] Folic acid deficient hematopoiesis is best diagnosed by measurement of RBC, not serum folate levels. Folate deficiency is treated with oral folic acid supplementation.

ii. Cobalamin or Vitamin B12 Deficiency

Vitamin B12 (cobalamin) deficiency is relatively uncommon in children, occurring most often in breastfed infants of mothers who are either strict vegetarians/vegans or who themselves have pernicious anemia (due to antibodies against intrinsic factor, which is required for absorption of vitamin B12).

Absorption of cobalamin occurs in the terminal ileum, so deficiency may develop from impaired absorption that occurs in conditions such as Crohn disease, pancreatitis, bacterial overgrowth, or surgical resection of the terminal ileum. Inborn errors of metabolism (e.g., transcobalamin II deficiency or methylmalonic aciduria) and, rarely, lack of intrinsic factor also may lead to deficiency in childhood. Classically, patients have a beefy, red tongue. Children who are ambulatory may complain of paresthesias or weakness, have an unsteady gait, or have decreased vibratory sensation and proprioception. Patients have a low serum vitamin B12 level, which may also be seen in some children with folic acid deficiency. Measurement of methylmalonic acid and homocysteine, which are the metabolic intermediates of B12 and folate, respectively, may help in the differential diagnosis. Both are elevated in cobalamin deficiency, whereas only homocysteine is increased in folate deficiency. Dietary B12 deficiency is treated with oral supplementation, whereas malabsorption usually requires repeated parenterally administered treatments.

iii. Other Causes of Megaloblastic Anemia

Other causes of megaloblastic anemia include certain medications that can affect the absorption or the metabolism of B12 or folate, such as methotrexate, zidovudine (AZT), 6-mercaptopurine (6-MP), hydroxyurea, sulfa drugs, or antiseizure medications (eg, carbamazepine, valproate, phenytoin, phenobarbital).[12]

Nonmegaloblastic Anemia/Inherited Bone Marrow Failure Syndromes

The congenital marrow failure syndromes are uncommon, but nevertheless important, causes of anemia and other cytopenias. With increased understanding of the clinical genetics of these disorders, it has become clear that there is a wide phenotypic spectrum, and these diseases must be considered in the differential diagnosis of children and adults with unexplained defects in hematopoiesis. Moreover, these conditions are not as rare as previously believed and may present as aplastic anemia or malignancy. Correct diagnosis is essential as it has implications for treatment, medical management, cancer screening, and family planning. While a comprehensive review of each disorder is beyond the scope of this textbook, the goal is to highlight insights into normal and disordered hematopoiesis, review cryptic presentations of these genetic syndromes, and provide useful references for the practicing pediatrician.

i. Diamond-Blackfan Anemia

Diamond-Blackfan anemia (DBA), originally described as a congenital hypoplastic anemia, is characterized by macrocytosis, reticulocytopenia, elevated levels of erythrocyte adenosine deaminase, presence of fetal membrane antigen i and a selective decrease or absence of erythroid precursors in an otherwise normocellular bone marrow. Diamond-Blackfan anemia typically presents in infancy, most commonly with pallor and lethargy, at an estimated incidence of 4 to 5 cases per million live births, and there is often a family history of the disease. Half of patients with DBA also present with physical abnormalities, including short stature, thumb abnormalities (classically, a triphalangeal thumb), craniofacial defects, and cleft lip/palate. Diamond-Blackfan anemia was the first disease to be linked to impaired ribosome function and is the founding member of a group of disorders now known as ribosomopathies. Several other IBMFSs (including Shwachman-Diamond syndrome and dyskeratosis congenita) and the 5q– syndrome (a subtype of myelodysplastic syndrome) have subsequently been linked to mutations in genes encoding for ribosomal proteins or for proteins required for normal ribosome function.

Up to 70% of patients with DBA have been identified as having mutations in ribosomal proteins, most frequently in RPS19. The fundamental question of how a mutation in a ribosomal protein, which would be expected to have widespread and diverse effects throughout an organism, can lead to selective defects remains a focus of investigation.[13] More recently, mutations in GATA1 have been identified in several patients with DBA suggesting that, in some cases, the disease may arise from causes other than defects in ribosomal protein genes. The disease is also known to have incomplete penetrance, as demonstrated both by the observation of siblings who carry the same mutation discordant for the presence of anemia, and by the occurrence of spontaneous remissions in affected patients. The current treatment for DBA includes corticosteroids and/or chronic transfusions; the only definitive treatment is hematopoietic stem cell transplantation (HSCT). With existing treatments, the overall survival of patients, as reported by the Diamond Blackfan Anemia Registry, is 75.1% at 40 years of age with a median overall survival of 58 years. Patients also experience a cumulative incidence of solid tumors or leukemia of 20% by age 46 years, suggesting that DBA is also a cancer predisposition syndrome. As our understanding of the pathophysiology of the ribosomopathies increases, the goal will be to translate these findings into novel therapeutic options for patients with DBA.

ii. Dyskeratosis Congenita

Dyskeratosis congenita (DC) is characterized by a triad of abnormal skin pigmentation, oral leukoplakia, and nail dystrophy; however, its spectrum has expanded considerably since its initial description in 1910 to include effects on every organ system, particularly the bone marrow. Almost 90% of patients with DC will eventually develop a cytopenia of 1 or more peripheral blood lineages. Bone marrow failure, which typically develops in the second or third decade of life, but can occur at birth or as late as the seventh decade of life, is the leading cause of death. The bone marrow abnormalities can evolve into myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). The original diagnostic triad is still important for identifying dyskeratosis congenita (DC); however, since the disease is now known to affect a variety of organs, the clinical suspicion must remain high when presented with a patient with bone marrow failure and unusual clinical findings. These findings may include early graying of hair or hair loss, short stature, developmental delay, blepharitis, periodontal disease, pulmonary fibrosis, esophageal stenosis, urethral stenosis, liver disease, or avascular necrosis of the hips or shoulders. The clinical diagnosis of DC can be challenging given its phenotypic heterogeneity, different modes of inheritance (X-linked, autosomal recessive, and autosomal dominant), and variable age of onset. However, despite the wide spectrum of the disease, ranging from classic DC to aplastic anemia, it is clear that the underlying pathology is due to defective telomere maintenance (the "telomeropathies"). In all characterized cases of DC, the causative mutations are in components of the telomerase complex. Mutations in 7 telomerase-complex genes have been identified in DC: DKC1, TERT, TERC, TINF2, WRAP53, NOP10, and NHP2. Two additional candidate genes, also involved in telomere maintenance or elongation, have recently been identified by whole exome sequencing: CTC1 and RTEL1. Therefore, functional assessment of telomere length, with the finding of telomere length to be less than the 1st percentile for age in leukocyte subsets, is highly sensitive and specific for the diagnosis. Telomeres are specialized protein-RNA complexes located at the ends of chromosomes that help stabilize chromosome ends, thereby preventing premature shortening, end-to-end fusions, translocations, or breaks.

Mutations in telomerase and shelterin components cause accelerated telomere loss. These mutations, in combination with environmental factors and possible second genetic hits, lead to premature cell death, stem cell depletion, and chromosome instability.[13] Ultimately, this cascade leads to the clinical phenotype of premature aging, bone marrow failure, nonhematologic abnormalities, and cancer. The actuarial risk of cancer in patients with DC is 40% by age 50 years with a particular risk for squamous cell carcinoma (head and neck, anogenital), MDS, and AML. Patients with DC are managed with supportive care and can respond to androgens and cytokines. The only long-term cure for the hematologic abnormalities is stem cell transplantation with a reduced intensity regimen. However, patients with DC have a much higher incidence of transplant-related morbidity/mortality, primarily from pulmonary toxicity and veno-occlusive disease. In addition, the relatives of patients who have DC who are being considered as donors should themselves be evaluated carefully for DC. The median overall survival of patients with DC is 43 years, although there is some correlation between genotype and both overall survival and age at cancer development.[14]

iii. Fanconi Anemia

Fanconi anemia (FA), the most common form of inherited bone marrow failure, typically progresses through several clinical stages over time. In the first stage, in infancy and early childhood, congenital anomalies, which can range from mild to severe, as well as developmental delay may be present. The most common malformations include short stature, hypopigmented or café au lait spots, thumb or radial ray abnormalities, microcephaly or hydrocephaly, structural renal anomalies, or hypogonadism. Within the first decade, patients may present with thrombocytopenia and macrocytosis before progressing to bone marrow failure, which is often when the diagnosis is made. During adolescence and adulthood, the risk of AML or MDS increases substantially. Additionally, a range of solid tumors, particularly squamous cell carcinomas of the head/neck and genitourinary tract, may occur in adults. Throughout life, the hematopoietic phenotype can change because of genetic reversion or clonal evolution; therefore, a high index of suspicion and a careful history, including a family history of cancer predisposition, is essential.[14] The diagnosis of FA is based on the sensitivity of FA cells to DNA interstrand cross-linking chemicals such as mitomycin C or diepoxybutane. Following exposure, cells from patients with FA develop characteristic chromosomal breaks. Of note, because of hematopoietic reversion, if the test is negative in lymphocytes but the clinical suspicion is high, the test should be repeated on patient fibroblasts. Once the FA diagnosis is established, the FANC genes can be sequenced for mutations. Except for rare mutations in the FANCB gene, located on the X-chromosome, all other FA mutations are autosomal recessive. Mutations in 16 genes have been identified in FA, the most frequent include FANCA, FANCC, FANCG, and FANCD2. Of note, FANCD1 is also known as BRCA2, which carries a strong predisposition to breast and ovarian cancers. The function of the FA proteins is to maintain genomic stability, mainly through repair of DNA interstrand crosslinks. The hypersensitivity of FA cells to DNA cross-linking agents, which results in increased numbers of chromosomal abnormalities, has significant implications for the treatment of these patients, whose median overall survival is only 33 years. Supportive care for FA-associated bone marrow failure includes androgen therapy (oxymetholone), hematopoietic growth factors, and transfusion support. Hematopoietic SCT is the only available curative treatment and outcomes are better with matched siblings (who should be screened for FA prior to transplant), younger patients, and reduced intensity conditioning regimens.

Unfortunately, HSCT does not cure the nonhematopoietic manifestations of FA and may further increase the risk of solid tumors. Gene therapy is being investigated for specific FA subtypes.

iv. Shwachman-Diamond Syndrome

Shwachman-Diamond syndrome (SDS, also known as Shwachman-Diamond-Oski syndrome) is a disorder of exocrine pancreatic dysfunction and bone marrow failure. Patients generally present with steatorrhea, growth failure, and recurrent infections. The most predominant hematologic abnormality is neutropenia, although anemia, thrombocytopenia, and pancytopenia can occur. Skeletal abnormalities (short stature, delayed appearance of normally shaped epiphyses, and progressive metaphyseal thickening/dysplasia) and poor growth are common in SDS patients. Patients without severe pancreatic disease may present later in childhood or as adults, and in some patients the initial manifestation of the disease may be with AML or aplastic anemia.[15] Although the diagnosis of SDS primarily relies on clinical findings, laboratory testing can help to confirm the diagnosis. Exocrine pancreatic dysfunction, which can be subclinical, can be confirmed by a low serum trypsinogen in patients less than 3 years of age or a low pancreatic isoamylase in patients greater than 3 years of age. Patients may also have a low fecal elastase or imaging evidence of a fatty pancreas. Genetic testing can be helpful in confirming the diagnosis of SDS (see below) but a negative test does not exclude it. It is essential to distinguish SDS from cystic fibrosis (the most common cause of exocrine pancreatic insufficiency in children), congenital neutropenia, and Pearson syndrome. In 90% of affected patients, this autosomal recessive disorder is due to mutations in the Shwachman-Bodian-Diamond syndrome (SBDS) gene. In the majority of cases, mutations are due to recombination of portions of an adjacent pseudogene with the SBDS gene. SBDS has been implicated in multiple biologic processes, including ribosome biogenesis, stabilization of the mitotic spindle, and cell motility. Recent studies have confirmed that SDS is a ribosomopathy caused by defective EIF6 recycling with a subsequent decrease in levels of translationally active mature 80S ribosomes. Developmental- and tissue-specific gene expression or translational requirements may cause differential sensitivities to decreased expression of particular genes involved in ribosome function, but this remains to be elucidated. Management of patients with SDS is directed at specific clinical manifestations. Clinically significant pancreatic dysfunction can be treated with oral enzyme replacement as well as supplemental vitamins A, D, E, and K. Pancreatic dysfunction improves with age in a subset of patients. Supportive care for the hematologic manifestations includes growth factors and transfusion support as well as aggressive management of infections in neutropenic patients. Patients with SDS tend to do better than other IBMFSs and HSCT is generally reserved for severe persistent or symptomatic cytopenia(s) or development of MDS/AML.[15]

v. Amegakaryocytic Thrombocytopenia

Congenital amegakaryocytic thrombocytopenia (CAMT), which presents in infancy and progresses to pancytopenia and bone marrow failure in later childhood, is a rare autosomal recessive disease characterized by an isolated, severe hypomegakaryocytic thrombocytopenia. Clinical manifestations can include petechiae at birth and intracranial hemorrhage, but unlike other IBMFSs, congenital anomalies are rare. Congenital amegakaryocytic thrombocytopenia is most commonly caused by mutations in MPL, which encodes for the thrombopoietin (TPO) receptor. In contrast to the activating MPL mutations seen in myeloproliferative neoplasms, CAMT mutations always lead to diminished or absent signaling of the TPO receptor.[16]

In general, loss-of-function mutations are associated with more severe thrombocytopenia and early-onset pancytopenia (CAMT type I). In cases with MPL gene missense mutations, patients have a transient increase in platelet counts in the first year of life (CAMT type II). The major treatment for bleeding is supportive care with platelet transfusions, and antifibrinolytic therapies for mucosal bleeding. Allogeneic HSCT is the only curative treatment option, but before this is considered, it is important to rule out Fanconi anemia and dyskeratosis congenita, both of which can initially present with isolated thrombocytopenia. Congenital a megakaryocytic thrombocytopenia has been proposed to be an ideal target for gene therapy.

vi. Pearson Syndrome

Pearson syndrome, also known as Pearson marrow-pancreas syndrome, is a multisystem disorder characterized by pancytopenia (anemia, neutropenia, and thrombocytopenia), ringed sideroblasts in the marrow, and exocrine pancreatic insufficiency. Patients often present in infancy or early childhood with failure to thrive, although clinical variants and atypical presentations do occur.[16] The syndrome is caused by large deletions or rearrangements of mitochondrial DNA leading to the absence of many proteins normally encoded by the mitochondrial genome. Heteroplasmy, the random distribution of mitochondrial DNA during cell division, is responsible for the high variability between patients and between different organs within the same patient. The disease can be diagnosed by mitochondrial DNA sequencing, distinguishing Pearson syndrome from SDS, as does the presence of ringed sideroblasts and marrow cell vacuolization. About half of patients die in infancy or early childhood due to severe lactic acidosis, sepsis, or liver failure. For patients who survive, the hematologic manifestations often resolve while the neurological and myopathic issues appear or worsen. Management is supportive and no specific therapy is currently available for individuals with Pearson syndrome or other mitochondriopathies. Although many IBMFSs are classically associated with only 1 cell lineage, patients frequently progress to frank pancytopenia and general bone marrow failure. IBMFSs generally present with macrocytic anemia, progressive pancytopenia, and congenital anomalies, particularly of kidneys and the radial side of the forearm. Short stature, intellectual limitation, and risk of malignancy are also characteristic. During the past several decades, the inherited mutations responsible for many of these syndromes have been identified, increasing the precision of diagnosis and detection of less severely involved patients, as well as furthering our understanding of the mechanism of marrow failure.[17]

CONCLUSION

Anemia is a reduction below normal in the concentration of erythrocytes or hemoglobin, measured per mm^3 or by volume of packed red cells per 100mL of blood. It occurs when the equilibrium is disturbed between blood loss (through bleeding or destruction) and blood production. Therapy for anemia is dependent on the underlying etiology. Iron deficiency anemia is the most easily preventable form of anemia. Management of inherited causes of anemia are largely supportive and based on clinical manifestations in the child including growth, nutrition, comorbidities, scholastic achievement, exercise tolerance, and quality of life.

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