Approach to severe anemia in children in the emergency room

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Anemia is a common clinical problem of children and is frequently first identified in the emergency department. Usually, the presentation is nonurgent, and a thorough work-up can be planned in consultation with a hematologist. However, some of the conditions warrant emergent attention and the emergency department physician needs to decide the diagnostic work-up and management before a hematologist sees the patient. This review summarizes the mechanisms of various types of anemias that can present in an emergency setting, and provides a brief overview of the diagnostic work-up and treatment strategies.

Anemia, in postneonatal age, is defined as a hemoglobin (Hb) concentration that is below the set reference standards for age, sex and race, and altitude levels. Until very recently, the diagnosis of anemia was based on the report of the 1958 WHO Study Group, with some later modifications, which arbitrarily defined Hb values below which anemia would exist (**Table 1**). However, more recently, a revised criterion has been proposed that defines anemia more precisely, and also takes into account the ethnicity of the patient [1,2].

To accurately diagnose and treat a child with anemia, it is important to define it precisely, understand the pathophysiologic mechanisms underlying different types of anemia and then plan a systematic approach towards the diagnosis and treatment.

Critical diagnostic evaluation and the collection of samples for necessary diagnostic tests must also occur prior to any intervention. Once transfused, the accurate diagnosis of intrinsic red cell abnormalities may be greatly delayed.

Pathophysiology of different types of anemia

Anemia can be a result of decreased production or increased loss/destruction of red blood cells. Thus, anemia can be classified as (**Box 1**):

- Disorders of red cell production, in which the production of red blood cell precursors is shut off due to either an inherited defect intrinsic to the red cell precursors or an acquired insult;
- Anemia due to ineffective erythropoiesis, where there is an increase in red cell precursors but they fail to achieve the normal maturation;
- Anemia from blood loss (acute and chronic);
- Hemolytic anemias, in which the red cells are destroyed in the circulation either due to an intrinsic defect or external injuries. The bone marrow responds to decreased Hb by increasing the production of reticulocytes.

Anemia in bone marrow failure syndromes

Bone marrow failure syndromes can be inherited or acquired disorders characterized by impaired hematopoiesis. They commonly cause pancytopenia in childhood, although isolated cytopenias are not uncommon. Approximately 25% are inherited and the rest are acquired [3].

Acquired aplastic anemia (AA) can be toxin-/drug-induced (benzene, chloremphenicol and so on) or idiopathic. The latter is thought to be an immune-mediated disease where an abnormal cytotoxic T-cell ($CD8^+$ cells) mediated injury to hematopoietic stem cells causes marrow aplasia [4]. The pancytopenia can be mild to moderate at presentation, but can gradually evolve into severe AA, defined on the basis of an absolute neutrophil count of less than 500/µl, a platelet count of less than 20,000/µl and a reticulocyte percentage of less than 0.5% [5]. Patients with severe AA are candidates for stem-cell transplant or immunosuppressive therapy, and transfusions should be given sparingly while the evaluation for transplant is in process.

Constitutional bone marrow failure syndromes (Fanconi anemia, dyskeratosis congenita and so on) should be suspected when physical examination reveals short stature, dextrocardia or skeletal abnormalities such as absent radius, absent thumb, syndactily or clinodactily.

Diamond–Blackfan anemia (DBA) is an inherited red cell aplasia. Patients usually present in early infancy. The exact causes are

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Table 1. Normal hemoglobin values in children.

Age group	Hemoglobin (g/dl)
Children 6 months to 6 years	11
Children 6–14 years	12
Adult males	13
Adult females, nonpregnant	12
Adult females, pregnant	11

Data taken from [1].

unknown, but mutations in the ribosomal protein gene, *RPS* 19 and *RPS* 24, have been described and account for approximately 25% of cases [6]. Anemia is present along with reticulocytopenia, and mean corpuscular volume (MCV) is increased. On bone marrow aspirates, erythroid precursors are absent or severely decreased. Approximately 25% of patients respond to steroids or immunosuppressive therapy. For the rest, stem-cell transplant offers the best chance of survival [7,8].

Transient erythroblastopenia of childhood (TEC) is an acquired red cell aplasia, likely secondary to a preceding viral illness [9]. The patients are generally in the 1–4 year age groups. Patients present with normocytic anemia and reticulocytopenia. Most patients recover spontaneously in 2–3 months, but some may require red cell transfusion due to severe anemia. It is important to distinguish TEC, which is a self-limiting illness, from DBA, which has a more prolonged course [10]. The MCV, fetal Hb and adenosine deaminase activity are elevated in DBA, but are normal in TEC.

Aplastic crises can occur in patients with congenital hemolytic anemias. Patients with sickle cell anemia, red cell enzyme deficiencies and hereditary spherocytosis can present with sudden and severe anemia, sometimes life threatening, from transient suppression of erythropoiesis. Unlike in TEC, such episodes are virtually always due to parvo B19 virus infections [11].

Anemia due to ineffective erythropoiesis

Iron-deficiency anemia

Worldwide, iron deficiency is the most common cause of anemia. Most of the iron requirements are met by recycling of the body stores and only small daily losses (1–2 mg/day) need to be replaced in the diet. Iron is absorbed from the duodenum and transported to the tissues bound to transferrin in plasma. Each molecule of transferrin binds two iron molecules, and the transferrin-bound iron is transported to the developing red blood cell precursors, where it binds to the transferrin receptor and enters the cell by endocytosis. Inside the cell, iron is used in the synthesis of Hb, and excess iron is stored as ferritin and hemosiderin. Some of the ferritin 'leaks' in to the serum, and thus serum ferritin is used as a surrogate marker of the body iron stores [12,13].

Iron deficiency anemia is suspected when anemia is associated with microcytosis (low MCV). Owing to ineffective erythropoiesis, there is a decrease in total red cell count and anisocytosis, reported as red cell distribution width (RDW) in automated blood cell counters; RDW is typically greater than 16 in iron-deficiency anemia (IDA) (normal: 12–14). The RDW value helps in differentiation of IDA from thalassemia trait, which also presents with anemia and microcytosis. In thalassemia, the red cell count is high, as there is a compensatory increase in erythropoiesis, and RDW is normal or minimally elevated. Hemoglobin evaluation will show an increase in HgbA2 and or HgbF in β-thalassemia trait and not in IDA. Serum iron profile (serum iron, transferring iron-binding capacity, ferritin and transferring saturation) helps in establishing the diagnosis.

If the iron deficiency is subclinical, both Hb and MCV may be normal. In such cases, a low ferritin, and an elevated free erythrocytic protoporphyrin, can be used as a marker of iron-deficient erythropoiesis [14]. Free erythrocytic protoporphyrin is normal in thalassemia trait. Transferrin saturation is also very useful. Normally transferrin is 20–50% saturated, and a value of less then 15% is suggestive of iron deficiency [15].

Treatment in these situations should aim at slow and gradual correction of Hb, and is usually accomplished by oral iron therapy at a dose of 3–5 mg/kg/day. The reticulocyte response is visible in 72 h and Hb rise within a week. The treatment should continue until at least 3 months after the normalization of Hb for the replenishment of stores. Packed red blood cell (PRBC) transfusion is rarely indicated unless Hb values are below 4 g/dl, the child is febrile and there is evidence of compromised hemodynamic status.

Lead poisoning

Historically, lead poisoning is included in the differential diagnosis of microcytic anemias; however, anemia and microcytosis in lead poisoning is mostly secondary to co-existing iron deficiency or thalassemia trait. RDW helps in differentiating the two [16]. There is a frequent

Box 1. Classification of anemia.

Disorders of red cell production

- Bone marrow failure syndromes
  - Acquired aplastic anemia
  - Inherited bone marrow failure syndromes
  - Diamond–Blackfan anemia
  - Transient erythroblastopenia of childhood
- Marrow replacement (malignancies, osteopetrosis and myelofibrosis)
- Impaired erythropoietin production (renal failure, inflammation and malnutrition)

Anemia due to ineffective erythropoiesis

- Iron-deficiency anemia
- Sideroblastic anemias
- Vitamin B12 and folic acid deficiency (megaloblastic anemias)
- Anemia in chronic disease

Anemia due to blood loss

- Trauma
- Bleeding lesions in the gastrointestinal/genito–urinary tract
- Menstrual blood loss
- Iatrogenic postoperative; prolonged stay in neonatal intensive care unit/pediatric intensive care unit

Hemolytic anemias

- Antibody mediated
- Red cell membrane disorders
- Defects in red cell metabolism (G6PD and other enzyme deficiencies)
- Hemoglobinopathies (thalassemia syndromes, sickle-cell disease, unstable hemoglobin disorders)
- Infection and other external injury to red blood cells

history of ingestion of peeling paint chips (which contain lead and taste sweet) and mud (so-called pica/pacophagia).

Anemia of chronic disease

Anemia of chronic disease is mostly secondary to systemic diseases, such as chronic inflammation (e.g., TB, chronic osteomyelitis), autoimmune disorders or malignancy. The anemia is usually mild to moderate and mostly normocytic and normochromic, although sometimes it can also be microcytic [17]. Serum ferritin is increased, while serum iron is decreased along with total iron-binding capacity. The serum levels of soluble transferrin receptors are high, indicating decreased iron supply, although they may not be as high as in iron-deficiency anemia [18]. The mechanism appears to be related to inadequate release of iron from macrophages. Hepcidin, a small peptide synthesized by the liver, can sense iron stores and regulate iron transport. Hepcidin production is increased in response to inflammatory cytokines (IL-6) and prevents the release of iron from the macrophages, causing hypoferremia [19,20].

Megaloblastic anemias

Although it rarely presents first in the emergency department, vitamin B12 and folate deficiency causing megaloblastic anemias are not uncommon. They are characterized by high MCV, frequently greater then 100 fl, and mild neutropenia and thrombocytopenia. Macro-ovalocytes and hypersegmented neutrophils are present on the peripheral smear. Macrocytes can be masked by coexistent thalassemia trait [21]. The cause can be nutritional (in vegans), as a result of short-gut syndrome or due to inherited disorders of the B12/folate pathway. Pernicious anemia due to intrinsic factor antibodies is extremely rare in children.

Hemolytic anemias

Immune hemolytic anemia

Immune hemolytic anemia (IHA) occurs when antibodies (IgG or IgM) bind to red cell antigen and cause red blood cell destruction. The antibodies may be produced as a result of alloimmunation, as occurs in mismatched blood transfusion or on an autoimmune process. Autoimmune hemolytic anemia (AIHA) can be primary (idiopathic) or secondary to a systemic disease. Furthermore, depending on the type and the thermal sensitivity of the antibody, AIHA can be the warm antibody type or the cold antibody type [22].

Warm antibody AIHA is caused by IgG antibodies, which bind strongly at room temperature. These antibodies are panagglutinins – that is, they react with all of the red cell antigens. IgG antibodies do not generally activate the complements, and red cells are phagocytosed by the splenic macrophages through their Fc receptors.

Cold agglutinin disease in children, although rare, can be life-threatening. In the majority of cases, it is transient and resolves spontaneously. It is caused by IgM antibodies, which bind strongly to the red blood cells at 0–4°C. These antibodies readily activate the complement system and can cause intravascular hemolysis [22]. The antibody is most often due to mycoplasma or viral infections; occasionally, drugs such as cephalosporins may also induce a cold antibody.

When AIHA is suspected, a positive direct antiglobulin test ([DAT] or Coomb's) would confirm the diagnosis. A complete blood count with a reticulocyte count, peripheral blood smear (PBS), bilirubin and lactate dehydrogenase are useful in assessing the severity of hemolysis. The typical blood count shows decreased Hb with reticulocytosis. The PBS shows spherocytosis, polychromasia and nucleated red blood

cells. LDH and bilirubin are elevated. The presence of hemoglobinuria indicates intravascular hemolysis. A positive Coomb's can be further 'split' to characterize the antibody type and complement fixation. In warm antibody type, DAT is positive for IgG. In cold agglutinin disease, the DAT with polyspecific sera may be negative, but monospecific DAT with anti-C3 at room temperature will be positive.

Treatment is based on the cause and the type of AIHA. The first step is stabilization of patients, as there can be severe volume depletion in intravascular hemolysis. It is important to recognize that in most cases of warm antibody AIHA, all blood units may test incompatible, as the antibody is nonspecific. Transfusions should not be withheld in search of the 'least incompatible unit', especially if Hb levels are dangerously low (e.g., 5 g/l) [23]. There is a very low risk of an allergic transfusion reaction [24]. Extended red cell genotyping and studies of antibody specificity should be undertaken prior to first transfusion. In cold antibody cases, the use of a bedside blood warmer is helpful.

Red cell membrane disorders

The red blood cell membrane disorders are a group of inherited conditions characterized by a defect in one of the red cell membrane proteins. The various entities in this group are hereditary spherocytosis (HS), hereditary elliptocytosis (HE), hereditary pyropoikilocytosis (HPP) and hereditary stomatocytosis (HSt).

In HS, a defect in ankyrin and/or band three proteins results in loss of membrane (spectrin) and alteration in the cell surface:volume ratio. The red blood cells assume a spherical shape and become less deformable. These rigid cells are trapped in the spleen and undergo further membrane loss until they are eventually destroyed [25].

Hereditary elliptocytosis is due to a point mutation in α-spectrin, the major red cell protein; there is a loss of spectrin–spectrin interaction, which causes elliptocytosis. HE is usually clinically silent. HPP is a related disorder in which two separate HE mutations are inherited, causing molecular defects in spectrin and a partial or severe spectrin deficiency [25]. The MCV is very low compared with HS or HE. Patients also have severe anemia and are transfusion dependent until splenectomy.

The clinical manifestations in red cell membrane disorders vary from being asymptomatic (HE), to severe transfusion-dependent hemolysis (severe HS and HPP). Most patients have mild to moderate anemia. Some patients present with jaundice and gallstones. Mild to moderate splenomegaly is common. The patients are at risk of some life-threatening complications, such as aplastic crises and acute cholecystitis from gall stones, the result of chronic hemolysis. In aplastic crises, red cell production is suppressed secondary to a viral infection, most commonly parvovirus B19 [26]. The patients present with severe anemia and reticulocytopenia. Packed red cell transfusion is required in severe cases.

The diagnosis of the membrane abnormalities is based on classical findings on PBS. Thus, in HS and HE, spherocytes and elliptocytes are seen on PBS, respectively. In HPP, the classical changes are marked poikilocytosis, elliptocytosis and low MCV. Osmotic fragility (OF) testing is the time-honored method of choice to confirm the diagnosis of HS. However, OF has low sensitivity and is not readily available in most laboratories. Thus, tests such as flow cytometry to detect band-3 deficiency or osmotic gradient ektacytometry are preferred in some institutions [26], including the Children's Hospital of Michigan (MI, USA) [27].

Red cell enzyme deficiency

Glucose-6-phosphate-dehydrogenase (G6PD) deficiency is the most common red cell enzyme deficiency in the world, with over 400 million affected. The deficiency is due to a genetic defect caused by mutations in *G6PD* gene, located on the long arm of the X chromosome. A deficiency of the enzyme causes reduced glutathione (GSH), exposing red blood cells to free radical injury [28].

Type A enzyme deficiency is seen in those with sub-Saharan African ancestry and is generally asymptomatic. The type B enzyme typically occurs in those of European and Asian ancestry. Patients usually have congenital nonspherocytic hemolytic anemia, often present from birth onwards. They can also present with exacerbations of hemolysis after an oxidant exposure.

G6PD deficiency was first described in patients experiencing hemolysis while being treated for malaria with primaquin [29]. In addition to antimalarials, sulfa drugs, infections and ingestion of fava beans (favism) are other common causes. In the past, a common oxidant exposure in children was from accidental ingestion of naphthalene-containing moth balls [30]. With an increasing influx of persons from Arabian countries, acute hemolysis from favism has supplanted naphthlalene exposure as the major cause of

G6PD-associated acute anemia at the Children's Hospital of Michigan. Once exposed, patients usually present with a severe drop in Hb and signs of hemolysis such as anemia with reticulocytosis, increase in bilirubin and hemoglobinuria. PBS shows significant anisocytosis and poikilocytosis with bite cells and helmet cells, the so-called moth ball cells. There is also marked polychromasia. Heinz bodies, which are the Hb precipitates in red cells, can be detected by supravital staining with methyl violet. The definitive diagnosis is achieved by carrying out a quantitative measurement of enzyme activity [31]. However, during acute hemolysis especially, testing may field a false-negative result because of high enzyme activity in young red cells (reticulocytes) [32].

Hemoglobinopathies

Hemoglobinopathies are a group of disorders characterized by a β- or an α-globin gene defect, which results in quantitative and/or qualitative abnormalities in Hb synthesis. Thalassemias are a quantitative abnormality of Hb synthesis, and the severity of anemia depends on the extent and type of mutation. However, they rarely present in an emergency setting, and patients are mostly managed on an outpatient basis.

Sickle-cell anemia is a qualitative abnormality of the globin chain, whereby valine is substituted by glutamic acid at the sixth amino acid position in the β-globin chain. As a result, the normal Hb tetramer assumes a sickled shape when deoxygenated. The sickle-cell Hb (HbS) thus formed results in hemolysis and vaso-occlusion [33].

Several variants of sickle-cell genotype can occur when a different second mutation is inherited from the second β-globin gene. HbS-β (0) thalassemia (no globin chain synthesis) has similar manifestation as homozygous sickle cell (SS) disease, while HbSC and HbS-β (+) (reduced globin chain synthesis) patients have a milder form of disease, with higher mean Hb levels. Patients with sickle-cell trait are usually asymptomatic.

Sickle-cell patients have a chronic anemia. In the homozygous (SS) state, the mean Hb is usually between 7 and 8 g/dl and is associated with reticulocytosis. The anemia is well compensated, and patients are asymptomatic, even with the low Hb. Various 'crises' can precipitate an acute drop in Hb, and may lead to hemodyanamic decompensation [34,35]. Two such crises are aplastic crises and splenic sequestration crises.

Aplastic crises occur when the compensation for chronic hemolysis and shorter red cell lifespan by an increased hematopoietic activity is arrested. Due to this cessation, there is an acute drop in Hb. Infections, particularly parvovirus B19, are the common cause of aplastic crises [36,37]. Besides the acute drop in Hb from their baseline levels, patients also suffer from severe reticulocytopenia. The treatment is an emergency transfusion of PRBC, especially if the Hb is below 5 g/dl or when there are signs of hemodynamic instability.

Splenic sequestration crises are due to vaso-occlusion in the spleen, causing a pooling of blood. As a result, there is an acute, severe drop in Hb, associated with thrombocytopenia, reticulocytosis and splenic enlargement, sometimes presenting as an acute shock-like condition. The crises generally occur at a younger age before the spleen is auto-infarcted [38]. The mortality is very high if the transfusion is delayed and emergent PRBC transfusion is indicated. The chances of recurrence are also very high.

Other hemolytic anemias

Microangiopathic hemolytic anemias (MAHA) are a frequent cause of sudden and severe hemolytic anemia, as in hemolytic uremic syndrome (HUS). The hemolyis is the result of a shear stress and fragmentation of red cells in the renal glomeruli damaged by extensive platelet-fibrin deposition – so-called microangiopathy. A related disorder is thrombotic thrombocytopenic purpura (TTP), which can have similar presentation but with minimal renal manifestations. TTP has now been shown to be due to an acquired deficiency of the von Willebrand protein-cleaving enzyme ADAMTS-13. In HUS, the Shiga toxins cause a sudden and abnormal release of ultra-large multimers of von Willebrand factor protein (ULVWF), exceeding the cleaving capacity of the normal ADAMTS-13 levels in these cases. The ULVWF attached to glomerular epithelial cells traps platelets, which results in thrombocytopenia [39]. The simultaneous presence of anemia, thrombocytopenia and renal failure should raise the suspicion of HUS; the presence of schistocytes on peripheral smear is confirmatory.

Another life-threatening disease to be considered in the differential diagnosis of severe anemia is hemophagocytic lymphohistiocytosis (HLH). HLH is characterized by hyperactivation and uncontrolled proliferation of macrophages, histiocytes and $CD8^+$ T cells [40]. The disease can be familial, due to mutation in the perforin gene, or an acquired form, which can occur secondary to infections (e.g., Epstein–Barr virus), malignancy or rheumatological diseases such as juvenile rheumatoid arthritis [41].

The diagnosis is based on the following clinical and laboratory features: prolonged fever, splenomegaly, bicytopenia, hypertriglyceridemia/hypofibrinogemia/hyperferritenimia and evidence of hemophagocytosis on bone marrow aspirates/biopsy [42].

Initial treatment consists of immunosuppresion with steroids and/or ciclosporin, and should be started immediately, as the disease can progress rapidly. Long-term cure in familial cases is achieved by stem cell transplant [41].

Diagnostic approach to a child with severe anemia

When a child presents with anemia, it is important to classify it appropriately. The automated blood counts provide many valuable parameters that help in the initial assessment of the cause of anemia – Hb, hematocrit, red blood cell count, MCV, RDW (which reflects the degree of size variation or anisocytosis), and the reticulocyte count. Review of the PBS is critical for identifying hemoglobinopathies, red blood cell membrane disorders and leukemias. Other critical information can be gleaned from a careful history and physical examination. Knowledge of race, ethnicity and geographic origin provide valuable clues. Sickle-cell disease is common in African–Americans. In general, hemoglobinopathies are common in people from the malaria belt, stretching from the Mediterranean Sea to South East Asia. G6PD deficiency is also common in this population. A history of blood loss must be actively reviewed, keeping in mind that the most common cause of iron-deficiency anemia in adolescent females is from menstrual blood loss. A simplified approach is described in **Figure 1**.

Diagnostic work-up

It is important for the emergency physician to recognize that samples for critical diagnostic studies must be obtained prior to any intervention, including transfusions. Contamination with transfused red cells may interfere with the diagnosis of inherited red cell disorders for extended periods of time and, in some cases, until after splenectomy [43]. Most hematologic disorders can be correctly diagnosed if samples of blood in EDTA or heparin and a serum sample are collected and set aside. In cases with suspected MAHA, HUS/TTP and other bleeding disorders, samples should be obtained for coagulation studies including VWF multimers and ADAMTS-13.

Treatment

The treatment for anemia is directed by its etiology. Emergency treatment is indicated in certain situations and depends on the patient's age, clinical condition, type, acuity and severity of illness, and presence of any homodynamic comprise. Overzealous and inadvertent PRBC transfusion may actually be detrimental [44].

Indications for blood transfusion

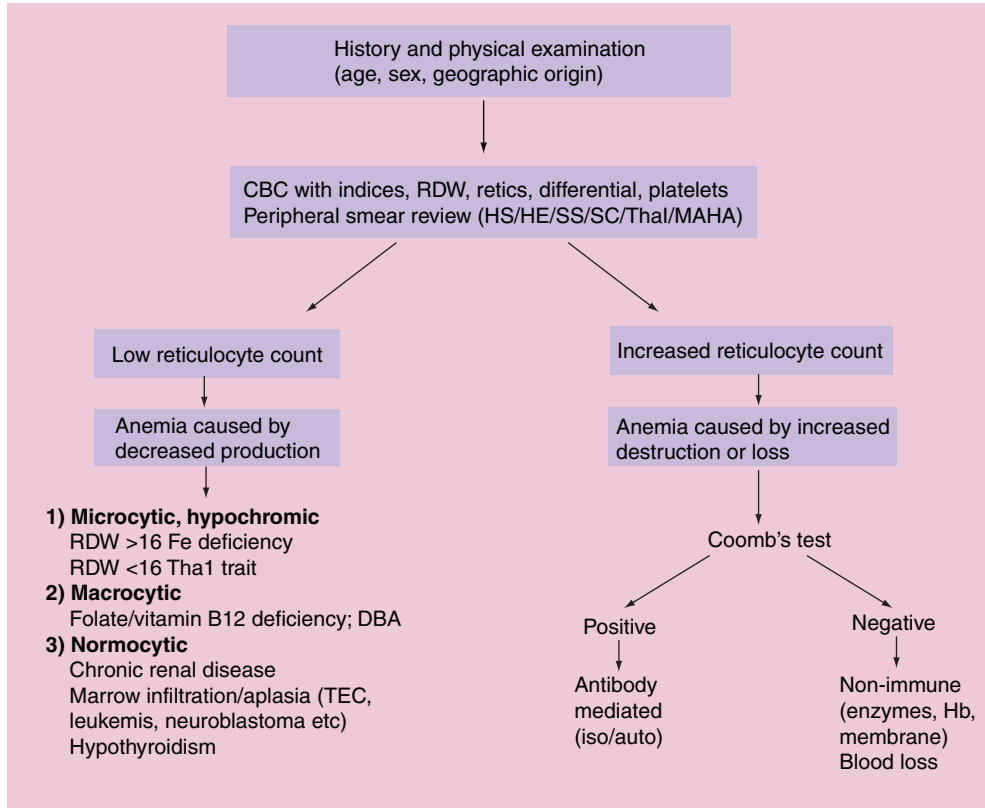
There are no well-defined guidelines for blood transfusion in pediatrics. Most of the indications are derived from adult literature [45]. The following are the general principles used in making such a decision:

- An acute drop in Hb below 7–8 g/dl or a rapid blood loss of more than 30–40% requires PRBC transfusions in most patients;
- In children with severe anemia developing over a course of time, PRBC transfusion has been shown to be safe and effective and results in an increase in the hematocrit of approximately 1% for each 1 ml/kg of PRBC transfused [46];
- In stable, critically ill children, the Hb cut off can be safely reduced to 7 gm/dl without increasing adverse outcomes [47];
- In hemoglobinopathies, red blood cells are transfused to prevent acute or chronic complications;
- In neonates, an increase in hematocrit to above 0.30–0.35 is required when respiratory distress is present.

Administration

Packed red blood cells are the product of choice for transfusion. Even in cases of emergency, whole blood is rarely used. Special processing may be required depending on the type of patients and the indication for transfusion. For example, an immunocompromised patient or a post-transplant patient will require irradiated product to avoid transfusion-related graft-versus-host disease. Leukoreduction is performed universally in the USA and most European countries, and helps to prevent alloimmunization and infection. A patient with sickle-cell disease will need sickle-negative blood. Transmission of viral infection, particularly cytomegalovirus (CMV), is a major concern with any transfusion. Leukoreduction reduces this risk, and a leukoreduced product is considered 'CMV safe'. However, certain groups of patients, for example, a CMV-seronegative post-transplant patient, or patients with severe immunodeficiency, require 'CMV-negative' product, which means that the donor has been screened to be CMV negative [48].

Figure 1. Investigation of anemias.



DBA: Diamond–Blackfan Anemia; MAHA: Microangiopathic hemolytic anemia; TEC: Transient erythroblastopenia of childhood; Thal: Thalassemia intermedia.

The usual dose of transfusion is 10–12 ml/kg of body weight. Thus, a 10-kg infant can be given 100–120 ml of blood. Assuming that the donor blood hematocrit is 65%, each 4 ml/kg of this transfused blood will raise the Hb by approximately 1 g/dl or hematocrit by 3%. This volume is transfused slowly over 1.5–2 h at room temperature. In cases with overt heart failure, it is preferable to transfuse in small aliquots of 5–6 ml/kg to prevent volume overload.

Special situations

Children with malignancies

Anemia is a very common complication of chemotherapy. Approximately 80% of children are anemic at some point in the course of their treatment, and approximately 95% require blood transfusion [49]. It not only has an effect on the quality of life, but may also affect treatment outcome. The current approach at most institutions, including ours, is to give blood transfusion for any drop in Hb below 8 g/dl. A mild to moderate drop in Hb is generally managed by close follow-ups.

Hemolytic anemia

In warm-antibody AIHA, methylprednisone is the initial treatment of choice. It is administered at a dose of 1–2 mg/kg every 6 h for the first 2 days, and then switched to oral prednisone. In most cases, improvement is observed after 2–3 weeks of therapy. If cold agglutinin disease is present, steroids are not effective, as they do not suppress the formation of cold-reacting IgM antibody. In childhood, cold antibody AIHA is self-limiting, and transfusion support is all that is needed. Intravenous immunoglobulin and plasmapheresis have been tried, with variable efficacy [50].

Sickle-cell disease

Three types of transfusions are indicated in sickle-cell disease: simple transfusion, exchange transfusion and chronic transfusion [51]. However, it should be remembered that sickle-cell patients are chronically anemic and are asymptomatic, and these patients do not require transfusion.

Executive summary

- Anemia is defined with respect to age, sex and race, and altitude levels.
- Anemia can be classified as:
  - Disorders of red cell production
  - Anemia due to ineffective erythropoiesis
  - Anemia from blood loss (acute and chronic)
  - Hemolytic anemias

Anemia in bone marrow failure syndromes

- Acquired and aplastic anemia usually present as pancytopenia.
- Diamond–Blackfan anemia (DBA) and transient erythroblastopenia of childhood (TEC) are important causes of anemia and reticulocytopenia in early infancy; TEC is transient and resolves spontaneously, while DBA has a protracted course.

Anemia due to ineffective erythropoiesis

- Nutritional anemias are the most common form of anemia worldwide.
- Along with anemia and microcytosis, iron-deficiency anemia is associated with decreased ferritin, transferrin saturation and increased iron-binding capacity.
- Other causes of microcytic anemia, such as thalassemia and anemia of chronic diseases, should be differentiated from iron-deficiency anemia.

Hemolytic anemias

- Hemolytic anemias can be due to disorders extrinsic to red cells, or due to intrinsic abnormalities, and usually present with anemia and jaundice.
- Immune hemolytic anemias are antibody-mediated and are the most common form of extrinsic hemolytic anemia. A positive Coomb's test is diagnostic.
- Hemoglobinopathies, membrane abnormalities (spherocytosis) and enzyme (G6PD) deficiency are the most common intrinsic causes of hemolytic anemia.
- Sickle-cell disease patients have a low baseline hemoglobin. However, several crises can precipitate an acute drop, which requires immediate intervention.
- Microangiopathic hemolytic anemias and hemophagocytic lymphohistiocytosis are rapidly progressive and fatal disease that need to be considered in the differential diagnosis of anemia.

Diagnostic approach to a child with severe anemia

- A thorough history and physical examination directs further work-up as appropriate.
- Inappropriate use of packed red blood cell transfusion can delay diagnosis or even be detrimental, and should be avoided. In emergencies, a sample of anticoagulated blood (EDTA, heparin), as well as serum, should be saved for later diagnostic studies.
- There are no well-defined guidelines for pediatric transfusion.
- Special processing of blood is required for various conditions and should be properly ordered.
- In patients with sickle-cell disease, exchange transfusion is indicated for stroke, acute chest syndrome and priapism. The goal is to maintain the sickle hemoglobin below 30%.

Future perspective

- Erythropoietin and blood-product substitutes may replace the need for packed red blood cell transfusion in the future, and are the areas of current research.

Simple transfusion is indicated when anemia develops acutely secondary to aplastic crises or sequestration of red blood cells in the spleen. The usual dose is 12 ml/kg of sickle-negative PRBC administered over a 4-h period. There is no recommendation for a target Hb level. However, usual practice is to keep the Hb below 10 g/dl post-transfusion to avoid complications secondary to altered viscosity [51].

Exchange transfusion is indicated in acute stroke, acute chest syndrome and priapism. The goal in all these cases is to keep HbS levels below 30% [51–53]. The amount of PRBC needed to be exchanged is given by the formula given in **Box 2**, where the estimated total blood volume is 80 ml/kg and the hematocrit level of the donor PRBC is 65%.

The development of alloantibodies is a common complication of transfusion. Various studies have reported an alloimunization rate of 20–40% in repeatedly transfused patients [54]. Thus, multiple units may have to be tested before a compatible unit is found, and sometimes it may be impossible to find a fully compatible unit.

Future perspective

The goals for the future are twofold. The first goal is to better define the criteria for intervention in

Box 2. Equation for the amount of PRBC that needs to be exchanged.

$$\frac{[(\text{desired hematocrit} - \text{original hematocrit} \times \text{total blood volume}]}{65 - [(\text{desired hematocrit} + \text{original hematocrit}) \div 2]}$$

pediatric patients with anemia, and the second is to find newer strategies to reduce the amount and risks of blood transfusion. Most of the guidelines for pediatric transfusion are based on adult literature and there is a lack of scientific evidence for some of the widely adopted practices. Well-defined pediatric studies are thus needed to strictly define the evidence-based criteria for transfusion.

Both erythropoietin and blood substitute are being investigated to minimize blood transfusions. Erythropoietin has been shown to be effective in patients with chronic renal disease, but its role in pediatric cancer patients receiving chemotherapy is still under investigation. Some studies have reported a beneficial effect in terms of reduction of PRBC and platelet transfusion, while others found no proven benefit. More randomized controlled trials are needed in pediatric populations to define the dose and duration of therapy [55–57].

Blood substitutes that can replace red blood cells as oxygen carriers are promising alternatives currently being investigated. They can meet the current blood product requirements and are free from any disease transmission risks. The two types currently under investigation are the Hb-based oxygen carriers and the perfluorochemical-based compounds. However, current products have several limitations. They have a very short half-life and thus can only be used for short-term replacement. Some of the agents are antigenic and can cause severe allergic reaction. Some may be unstable products [58]. Further research can provide us with more meaningful alternatives.

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