Red blood cells carry hemoglobin, which is measured to diagnose anemia. Normal hemoglobin values for children vary with age.

**The Evaluation and Classification of Anemia**

- Empowering You with Resources: 03
- Clinical Trials Offer Options for Patients and Families: 03
- Specialty Spotlight: MACC Fund Center: 09
- New Doctors Around the State: 10

*Children’s Hospital of Wisconsin*
**Why Pediatric Practice Matters**

At Children’s Hospital of Wisconsin, we know it is a privilege to treat your young patients.

**BY THOMAS SATO, MD**

Pediatricians derive a special satisfaction from working with children and adolescents. Not only do we work with patients who are rapidly changing and growing, but we also help bring along the next generation — people who might, in fact, take care of us one day.

At Children’s Hospital of Wisconsin, we are fortunate to have an academic arm that strives to find new, better techniques and therapies. We develop best-evidence protocols to ensure the best outcomes for patients and provide better care, with an emphasis on holistic and creative care that treats our patients with respect and avoids things like unnecessary tests.

Whether through a consultation or admission, we are prepared to give children the best of care here at Children’s — then get them back to their own pediatrician or family doctor.

We believe it is a privilege to take care of your young patients. And that’s what truly matters.

Best,

Thomas T. Sato, MD, FACS, FAAP
CEO, Children’s Specialty Group
Senior Associate Dean of Clinical Affairs,
Professor of Pediatric General and Thoracic Surgery,
Medical College of Wisconsin

“Not only do we work with patients who are rapidly changing and growing, but we also help bring along the next generation — people who might, in fact, take care of us one day.”

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**Children’s Research Institute at a glance**

**HUNDREDS**

of investigators, research trainees and technicians

**NEARLY $35 MILLION**

in external funding since 2015

**1,000+**

active clinical trials

**5**

AREAS OF PATIENT-CENTERED RESEARCH:

1. Cancer
2. Clinical effectiveness and outcomes
3. Community health and prevention
4. Neurosciences
5. Nursing
Empowering You with Resources
Specialty care guidelines now available online

At Children’s Hospital of Wisconsin, we focus on delivering what’s best for children. We know that sometimes means patients receiving care close to home from their own primary care physicians.

To support you, Children’s now offers specialty care guidelines as well as educational resources, for the following specialties:

- Adolescent medicine
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- Birthmarks and vascular anomalies
- Cardiology
- Dermatology
- Diabetes
- Endocrinology
- Imaging
- Neurosurgery
- Otolaryngology
- Sports medicine
- Craniofacial
- Dental and oral health
- Down syndrome
- Gastroenterology
- Neonatology
- Orthopedics
- Psychiatry
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Visit chw.org/careguidelines for more information about specialty care guidelines.

Clinical Trials Offer Options for Patients and Families
Children’s Hospital of Wisconsin trials advance research in cancer and blood disorders

Clinical trials have made tremendous progress in improving treatments and survival rates for children with cancer. By offering a range of clinical trials, Children’s Hospital of Wisconsin gives patients and families more options for fighting cancer and blood disorders.

With the support of the MACC Fund, we are able to offer many clinical trials through our own research programs as well as by participating in a number of research consortia. We have more than 150 open clinical trials, both investigator initiated and through consortia.

**BONE MARROW TRANSPLANT TRIALS**

**2256 TREO:** Allogeneic Hematopoietic Cell Transplantation for Patients with Nonmalignant Inherited Disorders Using a Treosulfan (IND 72479)

**“Clinical trials have made tremendous progress in improving treatments and survival rates for children with cancer.”**

Based Preparative Regimen \ ELIGIBILITY AGE: Up to 49 years \ COLLABORATING CENTER: Fred Hutchinson Cancer Research Center \ NCT02349906 \ LOCAL PI: Dr. Julie Talano

**Phase 2 Solid Tumor Immunotherapy Trial**

Using HLA-Haploidentical Transplant and Donor NK Cells: the STIR Trial \ ELIGIBILITY AGE: No age restrictions \ COLLABORATING CENTER: Froedtert Hospital \ NCT02100891 \ LOCAL PI: Dr. Monica Thakar

**CHP Alpha Beta (13BT051)**

Unrelated and Partially Matched Related Donor Peripheral Stem Cell Transplantation with Alpha/Beta T Cell and B Cell Depletion for Patients with Hematologic Malignancies \ ELIGIBILITY AGE: Up to 23 years

Continued on following page
CME Events

The Heart Summit
Congenitally Corrected Transposition of the Great Arteries
OCTOBER 5
8 A.M.–6:30 P.M.
CHILDREN’S HOSPITAL OF WISCONSIN
HERMA HEART CENTER
REGISTER: chw.org/theheartsummit

Connect with Children’s
There are no fees to attend these CME dinners.
NOV. 1, APPLETON
NOV. 8, MILWAUKEE
REGISTER: chw.org/connect

Best Practices in Pediatrics and Pediatric Emergency Medicine
MARCH 1–3, 2018
WISCONSIN D BELLS
LEARN MORE: chw.org/bestpractices

CONTACT FOR CME EVENTS:
Claire Connelly,
414-266-6242 or
Cconnelly@chw.org

U.S. News & World Report ranking by the numbers

200 medical centers evaluated
10 pediatric specialties evaluated
Children’s specialties ranked highly in every one, including
top 5 for Cardiology and Heart Surgery

HEMATOLOGIC MALIGNANCIES TRIALS
Epigenetic Reprogramming in Relapse AML: A Phase 1 Study of Decitabine and Vorinostat Followed by Fludarabine, Cytarabine and G-CSF (FLAG) in Children and Young Adults with Relapsed/Refractory AML. ELIGIBILITY AGE: 1–25 years. COLLABORATING CONSORTIUM: TACL \ NCT02412475 \ LOCAL PI: Dr. Michael Burke

A Phase 1-2 Multicenter Study Evaluating the Safety and Efficacy of KTE-C19 in Pediatric and Adolescent Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-4). ELIGIBILITY AGE: 2–21 years. COLLABORATING SPONSOR: KITE Pharma \ NCT02625480 \ LOCAL PI: Dr. Julie Talano

SOLID TUMOR TRIALS
SPOC-2012-001: Phase 1 Dose-escalating Study of MM-398 (irinotecan Sucrosofate Liposome Injection) Plus Intravenous Cyclophosphamide in Recurrent or Refractory Pediatric Solid Tumors. ELIGIBILITY AGE: 12 months-20 years. COLLABORATING CONSORTIUM: SPOC \ NCT02013336 \ LOCAL PI: Dr. Paul Harker-Murray

Learn more at chw.org/cancerclinicaltrials.

Hematologic Malignancies Trials

Epigenetic Reprogramming in Relapse AML: A Phase 1 Study of Decitabine and Vorinostat Followed by Fludarabine, Cytarabine and G-CSF (FLAG) in Children and Young Adults with Relapsed/Refractory AML. ELIGIBILITY AGE: 1–25 years. COLLABORATING CONSORTIUM: TACL \ NCT02412475 \ LOCAL PI: Dr. Michael Burke

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Learn more at chw.org/cancerclinicaltrials.
Anemia is defined as hemoglobin concentration that is more than two standard deviations below the mean for age (Table 1). Hemoglobin concentration varies considerably based on age and sex. Newborns have relatively high levels of hemoglobin due to intrauterine adaptation to a relatively hypoxic environment. During the first two months of life, hemoglobin production markedly decreases and a physiologic nadir occurs. The mean hemoglobin level rises gradually during childhood equally for boys and girls until puberty, when boys achieve a level approximately 20 percent higher than that of girls.

This article outlines the basic diagnostic approach to the evaluation of anemia.

PATHOPHYSIOLOGY OF ANEMIA
Anemia occurs as the result of one or a combination of four pathophysiologic mechanisms:
Acute blood loss (i.e., bleeding)
• Impaired production of red blood cells (i.e., iron deficiency, malignancy, aplasia)
• Increased destruction of red blood cells (i.e., immune-mediated hemolysis, hereditary spherocytosis, hemoglobinopathies)
• Sequestration of red blood cells within the spleen

HISTORY AND PHYSICAL EXAMINATION
The history and physical examination can assist in the evaluation of anemia and aid in determining the underlying etiology of anemia. Important components of the history and physical examination, as they pertain to the evaluation and diagnosis of anemia, are outlined below.

HISTORY
Pallor. A child with pallor is not necessarily anemic. Familial patterns of complexion are crucial because many patients are intrinsically pale. A careful evaluation of the child’s medical history is fundamental in the assessment of a patient with suspected pallor.

Diet. The dietary history is very important when evaluating a patient for anemia. Infants delivered prematurely, or exclusively breastfed infants without adequate iron supplementation from solids in the second half of their first year of life are at risk for iron-deficiency anemia. Toddlers who consume large amounts of cow’s milk and children and female adolescents who consume little meat are also at risk for iron-deficiency anemia. Patients and breastfed infants of mothers who follow a strict vegan diet may become deficient in vitamin B12.

History suggesting hemolysis. A neonatal history of hyperbilirubinemia supports a possible diagnosis of congenital hemolytic anemia such as hereditary spherocytosis. This can be further supported by a family history of anemia, splenectomy and/or cholecystectomy. Jaundice in a child of any age should prompt evaluation for hemolysis.

Medication and travel. Certain drugs, including antimalarial agents and sulfonamide antibiotics, can induce oxidant-associated hemolysis in the patient with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Other drugs can cause immune-mediated hemolysis (e.g., penicillin) or decreased red blood cell production (e.g., some anti-epileptic drugs). Travel history may suggest exposure to infections such as malaria.

PHYSICAL EXAMINATION
The general appearance of the child can provide clues to the severity and chronicity of the problem. Severe anemia that develops slowly over weeks or months, such as seen in iron deficiency, is often well-tolerated. Vital signs (including orthostatic blood pressure), height, weight and growth offer further insight into the severity and chronicity of the problem. Abrupt onset of anemia, such as is seen with acute blood loss or immune-mediated hemolytic anemia, can be associated with tachycardia and hypotension. Isolated pallor in a well-appearing child who does not have evidence of systemic disease is usually much less ominous than pallor noted in a child who is ill-appearing, has bruising, petechiae, lymphadenopathy and/or hepatosplenomegaly. Other clinical symptoms and physical exam findings that can be seen with anemia include: fatigue, headache, jaundice, tachycardia and flow murmur.

TABLE 1. Age-based norms for hemoglobin and MCV

<table>
<thead>
<tr>
<th>AGE</th>
<th>HEMOGLOBIN (g/dL)</th>
<th>MCV (fL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>16.5 (-2 SD 13.5)</td>
<td>108 (-2 SD 98)</td>
</tr>
<tr>
<td>2 months</td>
<td>11.5 (-2 SD 9.0)</td>
<td>96 (-2 SD 77)</td>
</tr>
<tr>
<td>3–6 months</td>
<td>11.5 (-2 SD 9.5)</td>
<td>91 (-2 SD 74)</td>
</tr>
<tr>
<td>6–24 months</td>
<td>12.0 (-2 SD 10.5)</td>
<td>78 (-2 SD 70)</td>
</tr>
<tr>
<td>2–6 years</td>
<td>12.5 (-2 SD 11.5)</td>
<td>81 (-2 SD 75)</td>
</tr>
<tr>
<td>6–12 years</td>
<td>13.5 (-2 SD 11.5)</td>
<td>86 (-2 SD 77)</td>
</tr>
<tr>
<td>12–18 years</td>
<td>Females 14.0 (-2 SD 12.0)</td>
<td>90 (-2 SD 78)</td>
</tr>
<tr>
<td></td>
<td>Males 14.5 (-2 SD 13.0)</td>
<td>88 (-2 SD 78)</td>
</tr>
</tbody>
</table>
**DIAGNOSTIC EVALUATION**

The components of the initial workup for suspected anemia are outlined below. All of these components are key to the classification of the anemia.

**CBC with differential.** A complete blood count (CBC) should be the initial laboratory test in a child with suspected anemia. This should always include a white blood cell (WBC) differential and a peripheral smear (discussed below). Based on age-based norms (Table 1), the presence or absence of anemia is then established. It is imperative to determine whether the patient has isolated anemia or if the anemia is accompanied by abnormalities in other cell lines (e.g., total WBC, neutrophils, lymphocytes, platelets). Anemia in combination with other cytopenias (e.g., thrombocytopenia, neutropenia) suggests a potentially more severe bone marrow disease.

**Reticulocyte count.** The reticulocyte count is essential to the classification of anemia. An elevated reticulocyte count indicates a bone marrow response to either increased red cell destruction (hemolysis) or acute or chronic blood loss. In cases of acute blood loss, there is a delay in bone marrow response of three to four days. Thus, in the setting of acute blood loss, the reticulocyte count is most helpful when the bleeding and subsequent anemia has been

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**New Physician Leader in Hematology/Oncology**

Respected research leader Cindy L. Schwartz, MD, MPH, joined Children’s Hospital of Wisconsin this year as medical director of Hematology/Oncology. She is also section chief of Pediatric Hematology and Oncology and a professor of Pediatrics at the Medical College of Wisconsin. After earning her medical degree at Brown University Program in Medicine, Dr. Schwartz completed a residency in Pediatrics and a fellowship in Pediatric Hematology/Oncology at Johns Hopkins University School of Medicine. She went on to earn a master's degree at Harvard School of Public Health. Dr. Schwartz brings her significant academic experience and expertise in the areas of Hodgkin lymphoma, osteosarcoma and childhood cancer survivorship to her new role at Children’s. She is board-certified in Pediatrics and Pediatrics-Hematology/Oncology and is a member of the American Pediatric Society.
present for more than a few days. Anemias are classified on the basis of the adequacy of the reticulocyte response. The reticulocyte count is 1–2 percent in the setting of normal hemoglobin. In patients with moderate or severe anemia, the reticulocyte count may appear elevated, but may be inadequate for the degree of anemia. The following formula needs to be used to calculate the corrected reticulocyte count: (reticulocyte count x hemoglobin)/normal hemoglobin for age. If the corrected reticulocyte count is greater than 2 percent, the bone marrow is producing red blood cells at an accelerated pace. Figure 1 displays a flow diagram that allows for the classification of anemia based on the reticulocyte response to the anemia.

**Mean cell volume (MCV).** The MCV reflects the red blood cell size and is vital to the classification of anemia. Normal standards for MCV are age-related (Table 1); a simple guideline is that the lower normal limit of MCV for children older than 6 months of age is 70 fL plus the patient’s age in years until the adult standard of 80–100 fL is reached. An elevated MCV is called macrocytosis and a low MCV is called microcytosis. Microcytosis is associated with iron deficiency, thalassemia, and long-standing anemia of inflammation. Macrocytosis is associated with vitamin B12 or folate deficiency, bone marrow failure syndromes (e.g., Fanconi anemia, Diamond-Blackfan anemia), and some cases of hypothyroidism. Figure 2 displays a flow diagram that allows for the classification of anemia based on MCV.

**Other abnormal cell lines.** Evaluation of the total WBC count, differential, and platelet count is imperative in the setting of anemia. For example, leukopenia, neutropenia and/or thrombocytopenia occurring in a patient with anemia of underproduction is suggestive of aplastic anemia or infiltrative bone marrow disease such as leukemia. Thrombocytopenia can occur in patients with iron deficiency, blood loss, inflammatory disease, infection, malignancy, or asplenia. Importantly, the interpretation of the etiology of anemia should not be done in isolation and should be considered within the context of the entire CBC.

**Peripheral blood smear morphology.** Abnormalities of red blood cell morphology are readily apparent upon peripheral blood smear review and provide clues to the etiology of anemia. For example, a predominance of spherocytic cells suggests hereditary spherocytosis or immune-mediated hemolytic anemia, whereas a predominance of small cells with exaggerated central pallor suggests iron deficiency anemia. The presence of immature leukocytes (i.e., blasts) associated with either a high or a low WBC count is suggestive of leukemia. Careful review of the peripheral blood smear by someone trained to evaluate cell morphology is crucial to the diagnostic evaluation of anemia.

**Other laboratory abnormalities associated with anemia.** Elevated indirect bilirubin, lactate dehydrogenase and aspartate aminotransferase levels are commonly seen in the context of hemolysis. Immune-mediated hemolytic anemia should be suspected when abrupt onset of anemia, jaundice, and/or reticulocytosis occur and spherocytes are seen on the peripheral smear. To investigate the etiology of hemolysis, a direct Coombs test to detect the presence of an autoantibody on the red blood cell surface should be done. A low serum iron level, elevated total iron-binding capacity, low percentage of iron saturation and decreased serum ferritin level support the diagnosis of iron deficiency. In the setting of chronic inflammation, the iron studies are often difficult to interpret since ferritin is an acute phase reactant. Hemoglobin identification should be completed to identify hemoglobinopathies such as sickle cell disease or thalassemia. Careful review of the newborn screen can also assist in the diagnosis of a hemoglobinopathy as the etiology of anemia. It is important to note that hemoglobin identification will be normal in patients with alpha-thalassemia trait; the presence of Bart’s
hemoglobin on the newborn screen supports this diagnosis in a child with mild microcytic anemia and normal iron studies. Assessment of red blood cell enzyme levels (i.e., G6PD) is recommended when infection- or medication-related hemolytic anemia is suspected in a male of Mediterranean or African descent. Macrocytic anemia is concerning in children and should always trigger prompt assessment for vitamin B12 or folate deficiency in addition to potential bone marrow failure disorders. When other cytopenias are seen, such as thrombocytopenia and/or neutropenia in addition to anemia, bone marrow aspirate and biopsy should strongly be considered to rule out malignancy, aplasia or other bone marrow disorders.

CONCLUSIONS
In summary, anemia is a nonspecific finding. Various pathophysiologic mechanisms that result in anemia need to be elucidated by a careful and methodological workup. Indices easily obtained from a peripheral blood draw can be suggestive of these different pathophysiologic mechanisms. As discussed above and illustrated in Figures 1 and 2, the reticulocyte count and MCV are extremely important indices that should always be interpreted in the context of anemia, and are key to guiding additional diagnostic workup. The urgency of the workup and treatment is dependent upon the degree of anemia in combination with the suspected etiology. The summary of a suggested stepwise diagnostic approach to the evaluation and classification of anemia is outlined in Figure 3.

REFERENCES
Correction

Karen L. Zorek, MD, is a pediatrician within Pediatric Gastroenterology at Children’s Hospital of Wisconsin. She was incorrectly listed as a pediatric gastroenterologist in our previous issue.
Pankaj Jain, MD, is a neonatologist at Children’s Hospital of Wisconsin–Fox Valley and an assistant professor of neonatology at the Medical College of Wisconsin.
Institute of Medical Sciences, Rohtak, India, MD
The Brooklyn Hospital Center, NY, Pediatrics
University of Alabama at Birmingham, Neonatology
Pediatrics

Lileth Mondok, MD, is a pediatric neurologist at Children’s Hospital of Wisconsin and an assistant professor in pediatric neurology at the Medical College of Wisconsin.
University of Philippines College of Medicine, Manila, Philippines, MD
Cleveland Clinic Foundation, Pediatrics

Jamie Weiser, OD, is a pediatric optometrist at Children’s Hospital of Wisconsin.
University of Missouri–St. Louis College of Optometry, OD
Children’s Mercy Hospital, Kansas City, MO, Pediatric Optometry

Alicia Chacon, OD, is a pediatric optometrist at Children’s Hospital of Wisconsin.
University of the Incarnate Word–Rosenberg School of Optometry, San Antonio, OD
University of Missouri–St. Louis College of Optometry, Pediatric and Binocular Vision

Retirements

Children’s Hospital of Wisconsin thanks these providers for their years of service.

John Gordon, MD | 1996–2017
Special Needs

Carl Weigle, MD | 1990–2017
Critical Care

Departures

Children’s Hospital of Wisconsin would like to thank the following providers for their contributions. We wish them well in future endeavors.

Neil Connor, MD, Critical Care
Garick Hill, MD, Cardiology
Jim Mueggenberg, MD, Critical Care
Nan Norrins, MD, Pulmonary Medicine
Diana Quintero, MD, Pulmonary Medicine
Children’s Around the State

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Delafield, WI 53018

Greenfield Clinic
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Greenfield, WI 53227

Kenosha Clinic
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Suite 101
Kenosha, WI 53142

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Mequon, WI 53092

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Neenah, WI 54956

New Berlin Clinic
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De Pere, WI 54115

The locations above are Children’s Clinics. We also see patients in other clinics in the following cities: Fond du Lac, Green Bay, Oshkosh, Racine and Iron Mountain, MI. We also perform surgeries in Marshfield.