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PEDIATRIC ROUNDS

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

Children's Hospital of Wisconsin

VOLUME 16 \ ISSUE 2 \ 2017

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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.

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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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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.

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

BONE MARROW TRANSPLANT TRIALS

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

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COLLABORATING CENTER: Children's Hospital of Philadelphia \ NCT02600208 \ **LOCAL PI:** Dr. Julie Talano

ACE CTL Trial: A Phase 1 Study using Multi-virus Cytotoxic T-Cells Following T-Cell Depleted Allogeneic Hematopoietic Stem Cell Transplantation for Prophylaxis Against Specific Pathogens-Adenovirus, Cytomegalovirus and Epstein Barr Virus \ **ELIGIBILITY AGE:** Up to 22 years \ NCT01535885 \ **LOCAL PI:** Dr. Julie Talano

The Safety and Efficacy of Prophylactic Defibrotide Administration in Children, Adolescents and Young Adults with Sickle Cell Disease Following Myeloablative Conditioning (MAC) and Haploidentical Stem Cell Transplantation Utilizing CD34 Enrichment and T-Cell (CD3) Addback (IND 127812) **ELIGIBILITY AGE:** 2–34 years \ **COLLABORATING CENTER:** New York Medical College \ NCT02675959 \ **LOCAL PI:** Dr. Julie Talano

BRAIN TUMOR TRIALS

A Phase 1 Study of Photodynamic Therapy (PDT) with Photofrin® (IND 104,613) for Poor Prognosis Recurrent/Refractory Malignant Brain Tumors **ELIGIBILITY AGE:** 6 months–18 years \ NCT01682746 \ **LOCAL PI:** Dr. Jeffrey Knipstein

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.

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

200 medical centers evaluated

10 pediatric specialties evaluated. Children's ranked highly in every one, including **top 5** **for Cardiology and Heart Surgery**

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DIABETES AND ENDOCRINOLOGY

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT CARDIOLOGY & HEART SURGERY 2017–18

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT RANKED IN 10 SPECIALTIES 2017–18

Source: *U.S. News & World Report*, 2017-18 Best Children's Hospitals

The Evaluation and Classification of Anemia

A diagnostic approach

BY AMANDA BRANDOW, DO, MS

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:

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- 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

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

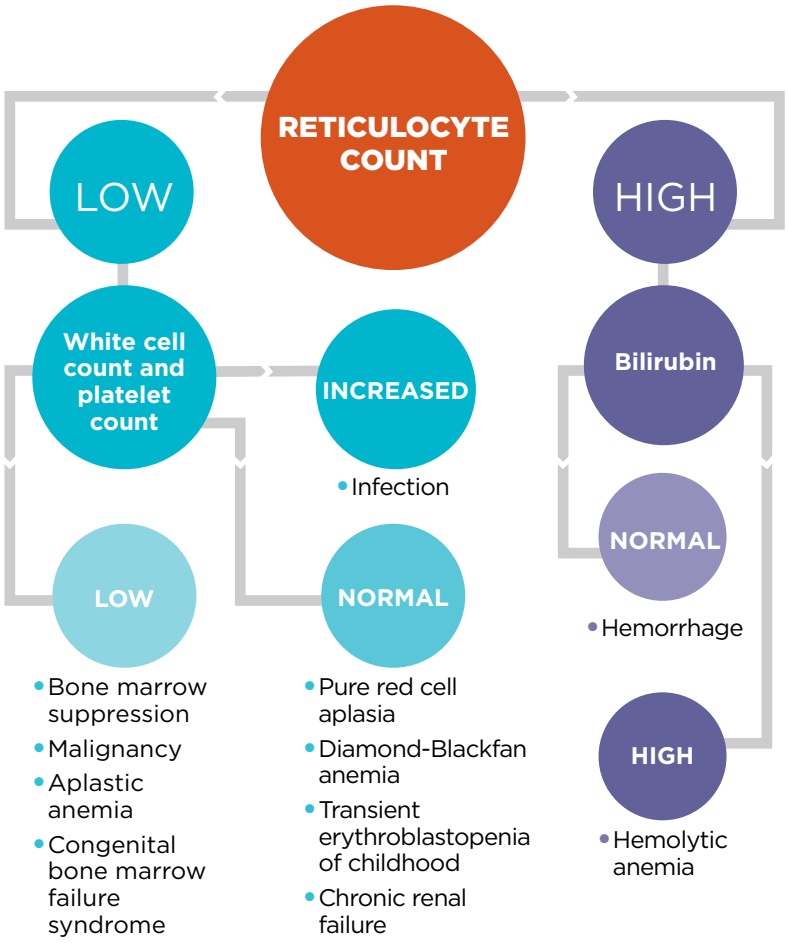
DIAGNOSTIC EVALUATION

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

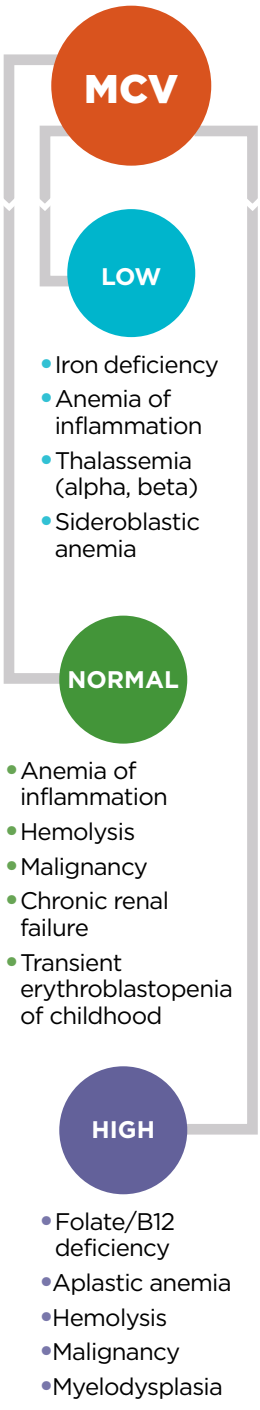
FIGURE 1. Framework for the classification of anemia based on reticulocyte count



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.

FIGURE 2.
Framework for the classification of anemia based on MCV



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. Thrombocytosis 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 sphercytosis 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**.

SPECIALTY SPOTLIGHT

MACC Fund Center

The MACC Fund Center at Children's Hospital of Wisconsin is one of the largest pediatric cancer and hematology programs in the country. Our interdisciplinary approach to diagnosis and treatment involves multiple physician specialties, as well as dedicated staff in nursing, social work, psychology, pharmacy, nutrition, child life and physical therapy. Patients have easy access to physician consultations within the hospital's subspecialties, including cardiology, nephrology, infectious disease and surgery.

Visit the MACC Fund Center at **chw.org/maccfundcenter**.

We also host the Medical College of Wisconsin's Pediatric Hematology/Oncology/Blood and Marrow Transplant Fellowship Program.

Learn more at **mcw.edu/Pediatrics/Hematology-Oncology-BMT/Fellowship.htm**.

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To find Children's programs for hemophilia and blood disorders, visit chw.org/medical-care/macc-fund-center/contact-us.

FIGURE 3. Stepwise Approach for the Classification of Anemia

1. **Determine presence** of anemia based on age-based norms
2. **Use MCV** to classify type of anemia (i.e., macrocytic, microcytic, normocytic)
3. **Obtain reticulocyte count** in ALL patients being evaluated for suspected anemia to determine bone marrow's response to anemia
4. **Evaluate other cell lines** (i.e., platelets, WBC with differential-neutropenia, lymphopenia)
5. **Direct workup** accordingly based on above information

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Cardiology

Sara Creighton, MD, is a pediatric cardiologist at Children's Hospital of Wisconsin and an assistant professor of pediatric cardiology at the Medical College of Wisconsin.

- University of Illinois College of Medicine, Peoria, MD
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- Medical College of Wisconsin, Pediatric Cardiology
- Pediatrics

Critical Care

Francis Kim, MD, is a pediatric critical care specialist at Children's Hospital of Wisconsin and an assistant professor of pediatric critical care at the Medical College of Wisconsin.

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- Stanford Hospitals and Clinics, Pediatrics
- Stanford Hospitals and Clinics, Pediatric Critical Care; Lucile Packard Children's Hospital Stanford, Pediatric Cardiac Critical Care
- Pediatric Critical Care Medicine

Hospital Medicine

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- Louisiana State University School of Medicine, Pediatrics
- Pediatrics

Imaging

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- Mallinckrodt Institute of Radiology, St. Louis, Nuclear Medicine, Neuroradiology and Pediatric Radiology

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Michael Hokensona MD, FAAP, is medical director of the Fox Valley neonatal intensive care unit at Children's Hospital of Wisconsin-Fox Valley and an assistant professor of neonatology at the Medical College of Wisconsin.

- St. George's University School of Medicine, MD
- New York Methodist Hospital, Pediatrics
- Women and Infants Hospital of Rhode Island, Neonatal-Perinatal Medicine
- Pediatrics, Neonatal-Perinatal Medicine

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.

KEY TO SYMBOLS: DEGREE RESIDENCY FELLOWSHIP BOARD CERTIFICATION

Neonatology

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

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University of Philippines College of Medicine, Manila, Philippines, MD
Cleveland Clinic Foundation, Pediatrics
Pediatrics

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University of Missouri–St. Louis College of Optometry, OD
Children's Mercy Hospital, Kansas City, MO, Pediatric Optometry

Ophthalmology

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

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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.