



PEDIATRIC FORUM

A journal of The Children's Medical Center of Dayton

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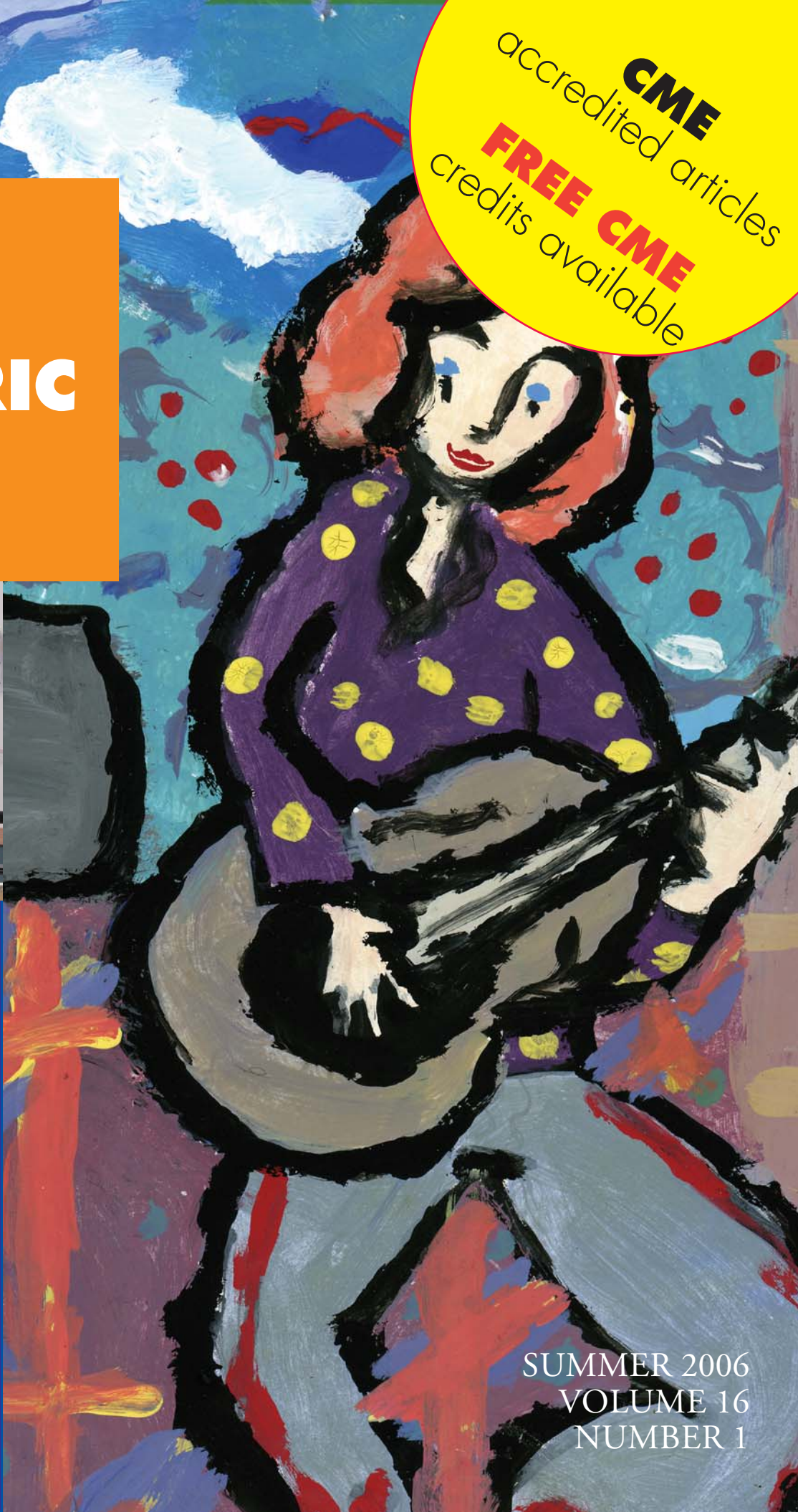
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SUMMER 2006
VOLUME 16
NUMBER 1



Pediatric Forum

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Pediatric Forum is produced for the professional staff and referring physicians of The Children's Medical Center of Dayton by the marketing communications department. The purpose of *Pediatric Forum* is to provide information and news about pediatric health care issues and to provide information about clinical services and management issues of Dayton Children's.

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This education activity is designed for pediatricians, family physicians and related child health care providers.

Educational objectives

- Articles will review commonly encountered clinical conditions and provide updates in pediatric medical and surgical care.
- Each individual article will have activity-specific learning objectives.

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Dr. King has nothing to disclose with regard to commercial support. Dr. King does not plan on discussing unlabeled/investigational uses of a commercial product.

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IMMUNIZATION UPDATE

2006



by
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at Dayton Children's and an
associate professor of
pediatrics at Wright State
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OBJECTIVES

After completing this article, the reader should be able to:

1. Understand current recommendations for meningococcal and pertussis immunizations in adolescents.
2. Discuss guidelines for the use of influenza virus vaccine in the pediatric population.
3. Understand recent vaccine developments in protecting individuals against infection with rotavirus, human papilloma virus and hepatitis A virus.

The Centers for Disease Control and Prevention (CDC) has declared childhood vaccine utilization in the United States as one of the top ten public health achievements of the last century. New vaccines and new vaccine recommendations have appeared with increasing frequency in the recent past. Additionally, the vaccine schedule has “grown up,” recognizing that vaccines are not solely indicated for young children, but are part of an integrated continuum across other age groups. This article reviews recent and future vaccine developments pertinent to the practicing pediatrician.

Meningococcal-conjugate vaccine (MCV)

Young children, particularly infants, and adolescents aged 15 to 17 years, are at highest risk for meningococcal infection. A conjugate polysaccharide-protein vaccine (serogroups A, C, Y and W135) is recommended for adolescents aged 11 to 18 years (ideally at the 11 to 12 year preadolescent visit or for those entering high school). College entrants and other high-risk groups should receive MCV. As compared to polysaccharide vaccines, conjugate vaccines could provide a more protective immune response by inducing more robust T-cell lymphocyte involvement rather than relying on B-cell lymphocyte memory.

Varicella vaccine

All children aged 12 months and older should be vaccinated against varicella. As varicella vaccination rates have increased in the United States, the incidence of chickenpox cases has diminished. Coverage rates have reached less than 90%; however, the proportion of cases occurring in vaccine recipients has increased recently. A second dose of this vaccine is likely necessary to further reduce the burden of disease. The FDA has approved an optional second dose for children aged 12 months to 12 years, given at least three months apart. The CDC will revisit consideration of a routine second dose.

Measles-mumps-rubella-varicella vaccine (MMRV)

MMRV vaccine recently was approved. To induce protective immunity, the vaccine contains a higher amount of attenuated varicella virus. This vaccine should be used instead of MMR and may be utilized for the second dose, perhaps making consideration of the second varicella vaccine dose moot.

Tetanus-diphtheria-acellular pertussis vaccine (Tdap)

Since 1976, the number of reported pertussis cases in the US has increased 20-fold. The greatest increases have been noted in adolescents and young adults. Importantly, these individuals may transmit infection to the young infant who is at higher risk for significant disease and mortality. Tdap is recommended to replace Td as single-dose boosters in adolescents, preferentially given at the 11 to 12 year visit. Tdap is preferred when Td is indicated, should be given only once to teens, and can be administered concomitantly with MCV. A five-year interval between Td and Tdap is encouraged; although the interval may be shortened in certain situations, such as community outbreak. Boostrix (GlaxoSmithKline) is licensed for individuals aged 10 to 18 years and Adacel (sanofi-pasteur) for those aged 11 to 64 years.

Influenza vaccine

Beginning with the 2004-2005 influenza season, it was recommended that all healthy 6- to 23-month-old infants and children receive annual trivalent influenza vaccines because of recognized increased morbidity, potential mortality and hospitalization rates. Children not previously vaccinated should receive two doses at least a month apart. Other recognized high-risk groups (people aged 2 to 64 years with underlying chronic medical conditions, women pregnant during the influenza season, health care workers with direct patient contact, individuals greater than 65 years of age, caregivers and household contacts of children less than 6 months) should be vaccinated annually. Recent expansions of the guideline stress the importance of immunizing close contacts of healthy children less than 2 years of age. Any underlying condition that compromises respiratory function or the handling of respiratory secretions or that increases the risk of aspiration was added to the 2005 CDC recommendations as additional high-risk conditions. Influenza vaccine shortages can have major impacts on effective vaccine delivery. Live attenuated influenza virus vaccine (Flumist, MedImmune) may be used in healthy people aged 5 to 49 years.

Hepatitis A virus (HAV) and hepatitis B virus (HBV) vaccines

Routine HAV vaccination in children who live in populations with high rates of hepatitis A infection was recommended by the CDC in 1996. This strategy has resulted in overall lower national rates. To further minimize HAV infection, the possibility of universal HAV vaccine coverage has been discussed and continues to be reviewed. The FDA recently approved HAV vaccine (VAQTA, Merck) for use beginning at 12 months of age.

The importance of administering the birth dose of HBV vaccine must be further emphasized. Currently, less than 50% of HbsAg + mothers are identified for effective hepatitis preventive strategies. It is recommended that a birth dose of HBV vaccine be given unless the physician knows that the mother is HbsAg negative and writes an order not to give the birth dose.

Rotavirus vaccine

A live human-bovine reassortant rotavirus vaccine was recently approved by the Food and Drug Administration. Subsequently, recommendations for the use of this vaccine were issued by the Advisory Committee for Immunization Practices of the CDC and by the American Academy of Pediatrics. In prelicensure studies, this vaccine was effective both in preventing severe rotavirus gastroenteritis and in minimizing hospitalizations for severe rotavirus gastroenteritis. In these studies, the vaccine had an exceptional safety profile demonstrating no increased risk for intussusception in vaccine recipients when compared to placebo recipients. The vaccine should be administered as a three-dose series for infants between the ages of 6 and 32 weeks. Doses of the vaccine are administered at 4-10 week intervals beginning at 6-12 weeks of age.

Human papillomavirus virus (HPV) vaccine

HPV infections are associated with potential development of malignancy (cervix) and with sexually transmitted diseases. A bivalent HPV vaccine (GSK) containing HPV-16 and -18 virus-like particles and a quadrivalent vaccine (Merck) composed of HPV-11, -18, -6, and -11 virus-like particles have been developed (HPV-6 and HPV-11 account for 90% of genital warts). The former vaccine will target females aged less than or equal to 10 years of age while the latter will target a population aged 18 to 45 years of

both genders. The HPV knowledge base of the public and of primary care practitioners likely will need to be augmented in order to allay concerns that vaccination will be utilized to protect against STDs. Recommendations on the use of these vaccines are expected soon.

Undoubtedly, changes in the vaccination schedule and further introduction of new vaccines will occur with regular frequency in the years ahead. Modifications on the use of older vaccines will likely occur as practitioners increase their experience with these agents. The practitioner's role is to administer these effective tools in disease prevention. It is a further responsibility to educate the public on the importance of timely receipt of immunizations to prevent illness between both the pediatric population and other age groups.

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CME QUESTIONS

1. Which is an indication for vaccination annually with trivalent influenza vaccine?
 - a. Healthy infants 6 months to 23 months of age
 - b. Infants with neurological conditions that can compromise swallowing and are at risk for aspiration.
 - c. Pregnant women during the influenza season
 - d. a and c
 - e. All of the above
2. As pertains to hepatitis A virus infection, which of the following is true?
 - a. The incidence of hepatitis A virus infection in the last decade has not decreased.
 - b. Hepatitis A vaccine cannot be given to children aged 12-24 months.
 - c. Current hepatitis A vaccine strategy targets children living in areas of the country with high rates of hepatitis infection.
 - d. It is currently recommended that all infants should be vaccinated against hepatitis A virus.
3. Future utilization of a vaccine (both the bivalent and the quadrivalent formulations) against infection with human papillomavirus:
 - a. May potentially decrease the incidence of cervical cancer in women
 - b. Will target only females
 - c. Could decrease the occurrence of condylomas (genital warts)
 - d. a and c
 - e. All of the above
4. Varicella vaccine
 - a. Utilization has resulted in some recent chickenpox outbreaks that reflect breakthrough varicella infections in a growing proportion of previously vaccinated children.
 - b. Use has not significantly diminished the overall number of cases of chickenpox nationwide.
 - c. Is not approved by the FDA for a second dose in children aged 2 years to 12 years.
 - d. Is currently not available as a combination vaccine with MMR.

NECK PAIN AND STINGERS IN THE ATHLETE



by **Todd Maugans, MD**

Dr. Maugans is a pediatric neurosurgeon with Dayton Children's. He is board certified in neurosurgery and is a former board-certified family practitioner.

OBJECTIVES

After completing the article, the reader should understand:

1. The important differential diagnosis that directs the evaluation and management of the athlete with neck pain.
2. Pathophysiology, evaluation and management of the athlete who has sustained a stinger.
3. "Red flag" situations in the evaluation of athletes with potential neck or brachial plexus injuries that demand immediate medical attention or referral to a pediatric neurosurgeon.

Although concussions are the most frequent injury of the nervous system in athletes, injuries to the cervical structures and brachial plexus also occur frequently. Contact sports participants are especially at risk. It is paramount to have an understanding of a differential diagnosis and a rational approach to the athlete with cervical pain as well as understand the pathophysiology and management of "stingers."

Three scenarios are possible in athletes presenting with cervical pain: 1) the athlete becomes non-ambulatory because of the severity of pain, associated neurological problems or other injuries; 2) the injured athlete has the acute onset of neck pain but can leave the field or arena in an ambulatory fashion; or 3) the athlete exhibits subacute or chronic cervical pain. Table 1 outlines the differential diagnosis for the athlete presenting with cervical pain. In general, it is wise to apply this differential to all three categories of injured athlete. Unstable cervical spine injuries—those that can produce neurological injury, spinal instability or chronic pain—can be the ultimate diagnosis in any three of the categories of the injured athlete. Typically, it is best to assume the worst-case scenario, a fracture of the cervical spine, until this can be ruled out.

The conditions in Table 1 are ordered in terms of lowest frequency, but of highest risk to the athlete. With this in mind, the most prudent management to be employed in all scenarios is immediate removal from play and application of a hard cervical collar. Examples of appropriate hard collars include the "Stiff Neck," "Philadelphia," "Miami Jay" or "Aspen" collars. Soft collars are of no benefit since even hard cervical collars provide only limited protection against excessive cervical movement. If lower spinal injury is suspected or the patient has neurological complaints or findings, he or she should be placed on a backboard and transported to a health care facility for immediate evaluation and management.

Causes of neck pain in the athlete

- Cervical fracture (with or without spinal cord injury)
- Dissection of carotid or vertebral artery
- Ligamentous injury of the cervical spine
- Herniated intervertebral disc
- Muscular contusion or hematoma
- Superficial soft tissue injury

Table 1

The mechanism of injury, location of pain, quality of pain and physical examination are all important components of the evaluation of the patient with cervical pain. A patient who has sustained a violent flexion extension injury is more likely to incur a significant spine injury than an athlete who has reported a minor blow to the cervical region. While the former type of injury may produce severe posterior neck pain, bilateral upper and lower extremity sensory and motor alterations, the latter may produce only localized pain to the dorsal lateral cervical musculature. Midline dorsal tenderness over the cervical spinous processes is considered a "red flag" for significant spinal injury. Spine fracture should always be ruled out radiographically in an athlete with such a complaint or finding.

Anterior neck pain in the region of the carotid artery also raises the possibility of dissection. Although this is a very uncommon injury, it places the athlete at risk for acute stroke with catastrophic outcome if not appropriately diagnosed and managed.

An examination of the cervical spine includes inspection and palpation. Range of motion should be carried out only if the patient is awake, alert, neurologically intact, without other distracting injuries (eg, a sprained ankle) and he or she indicates that the pain is paramedian or lateral on palpation. When in doubt, maintain the patient in a cervical collar and defer range of motion examination until appropriate radiographic evaluation can be performed.

Although the radiologic evaluation for significant neck pain has historically required anteroposterior (AP), lateral and odontoid radiographs of the cervical spine, a fine-cut CT scan of the cervical spine with 3-D reconstruction is rapidly supplanting plain films. The fine-cut CT scan's sensitivity and specificity for significant cervical spine injury is still being studied, but its clinical utility is powerful. When in doubt, a consultation with a radiologist or pediatric neurosurgeon can be useful. If imaging identifies a spinal fracture or subluxation, or any neurological injury is present, the patient should be immediately referred for management by a pediatric neurosurgeon.

In the event that a significant spine or spinal cord injury is excluded by appropriate clinical examination and/or appropriate imaging studies, the player can be treated in a conservative fashion as likely having a strain or sprain. Until the athlete's symptoms are completely resolved with full and passive range of motion and no tenderness exists on palpation, it is important that the athlete refrain from play. Non-steroidal anti-inflammatory medications, ice and rest (in a hard cervical collar only if it affords comfort) are tried and true modalities. Physical therapy can be an important adjunctive therapy, especially to help the athlete strengthen weak cervical muscles and increase flexibility which are both paramount to the prevention of re-injury. Recurrent or chronic pain demands referral to a pediatric orthopedist or neurosurgeon.

Stinger

Stingers, also known as "burners," are defined as a neuropraxic (nonstructural) injury of the upper portion of the brachial plexus. Stingers most typically involve the C5 and C6 nerve root distributions, regarding sensory and motor deficits. They may occur in as many as 25% of all football players and wrestlers per season. The injury occurs either via compression of the brachial plexus with lateral flexion laterally, or stretch of the brachial plexus with contra-lateral flexion. Tackling and wrestling take-down maneuvers are the highest risk activities for producing such trauma.

Typically, the stinger clinically presents as unilateral stinging or burning quality pain in the shoulder region, perhaps extending down into the forearm and first and second digits. A spinal cord injury is implied until proven otherwise when there is involvement of more than one extremity, involvement of an entire upper extremity, less than $4/5$ motor strength and anesthesia. Posterior neck pain implies a spine injury rather than a stinger; pain or tenderness in the ipsilateral supraclavicular fossa occurs commonly with stingers.

CME QUESTIONS

- 5.** The most appropriate first step in the management of all athletes who leave the field of play complaining of new-onset neck pain, regardless of severity, is:
 - a. Application of a cervical collar
 - b. Cervical range of motion assessment
 - c. Disallowing return to play until the problem is thoroughly evaluated and managed.
 - d. Referral to a tertiary care center

- 6.** Dorsal midline cervical pain and tenderness is most concerning for the possibility of:
 - a. Brachial plexus injury
 - b. Spinal cord injury
 - c. Cervical fracture
 - d. Cervical muscular hematoma

- 7.** Appropriate evaluation of the patient with severe neck pain includes all but the following:
 - a. Range of motion assessment
 - b. Defining mechanism of injury
 - c. Neurological examination
 - d. Radiographic imaging of the cervical spine

- 8.** Red flags in assessing the athlete with a suspect stinger includes all the following except:
 - a. Bilateral symptoms
 - b. Neck pain
 - c. Burning sensation in the shoulder region
 - d. Weak grip

The evaluation of the stinger is very similar to cervical pain. A very careful history, detailed neurological examination of the extremities and appropriate neuroimaging is necessary in most cases. If cervical pain is involved, a cervical spine or spinal cord injury needs to be ruled out through appropriate imaging and modalities. If the athlete merely sustains a transitory (less than 24 hours) burning sensation to the shoulder with a normal neurological examination and cervical examination, neuroimaging is not required to rule out cervical spine fracture, subluxation or spinal cord injury.

The management of stingers is based on general sports medicine concepts. The most important principle is not allowing the athlete to return to play until the symptoms are entirely resolved. Rest, icing and non-steroidal anti-inflammatory medications may be helpful. As with muscular cervical injuries, a short course of physical therapy aimed on strengthening, and improving range of motion of the cervical musculature is paramount to mitigate the forces that could reproduce the brachial plexus insult when the athlete returns to play.

Several “red flags” apply to athletes presenting with stingers. First, when evaluating the preteen or young teenaged athlete, be certain to rule out spinal stenosis. It is recognized that a small spinal canal (and associated neural foraminae where the nerve roots exit) places the player at risk for recurrent stingers and possibly for spinal cord injury. This is done radiographically, assuring that the ratio of spinal canal, width of vertebral body at the mid-cervical level, is at least 0.80. Second, monitor the athlete who sustains recurrent stingers, especially in a single season. Such athletes should be considered for removal from play since he or she has about an 85% chance of another stinger. Although permanent neurological injury is unlikely with recurrent stingers, the symptoms can become more protracted and imply a “vulnerability” that can be mitigated only by ceasing to participate in the particular sport. Third, if symptoms last more than 24 hours, referral to a pediatric neurosurgeon is recommended to rule out possibilities that include a herniated intervertebral disc, nerve root avulsion or brachial plexitis. Finally, the athlete who has symptoms that are bilateral and/or extend beyond the C5 and C6 distributions (eg, outside of the distribution of a single shoulder, lateral arm and forearm region or the first two digits) should be referred to a pediatric neurosurgeon for consideration of a more significant spinal cord, brachial plexus or peripheral nerve injury.



by Wilson King, MD

Dr. King is a second year pediatrics resident at Wright State University Boonshoft School of Medicine. He comes to Dayton Children's from Cincinnati, Ohio, where he also attended medical school.

OBJECTIVES

After reading the article, the reader should:

1. Know the incidence and prognosis for IPEX.
2. Recognize the clinical presentation for IPEX.
3. Understand the pathophysiology of IPEX.
4. Know the current treatment modalities for IPEX.

CASE STUDY: IPEX SYNDROME

History of present illness

AF is a 3-month-old white male who presented in Dayton Children's emergency department with a two-and-a-half-week history of progressive worsening diarrhea and a three-day history of nonbloody, nonbilious emesis. The diarrhea was described as watery, yellow/green and occurred up to 10 episodes per day. No fever or abdominal pain was reported. Urine output was decreased, but he continued to have good PO intake, taking Isomil DF. No sick contacts were reported and patient did not attend day care. Patient did not have any significant travel history, antibiotic exposure or well-water exposure. He was hospitalized overnight for vomiting and dehydration one month ago.

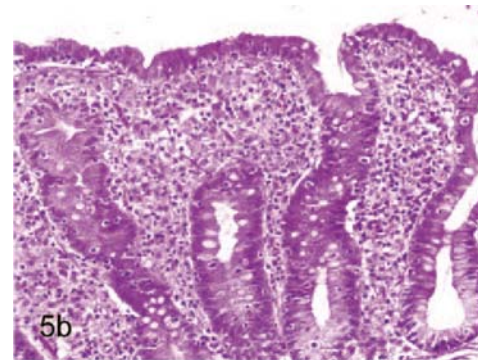
Past medical history and medications

Past medical history was significant for neonatal diabetes diagnosed at the first day of life, anemia, GERD, failure to thrive and eczema. He was on a scheduled q6 regimen of NPH and sliding scale of Novolog. He also received Fer-in-sol and Procrit for his anemia, Zantac and Reglan for GERD and Westcort. No drug allergies were documented.

Birth history and family history

His birth history was significant for emergent c-section secondary for fetal distress at 36 weeks from a 26-year-old G2P2 GBS negative, HSV negative mother. His initial blood glucose was 550. Patient was hospitalized in Dayton Children's Newborn Intensive Care Unit (NICU) for three weeks for evaluation and management of neonatal diabetes by pediatric endocrinology. The patient subsequently was diagnosed with

FIGURE 1
Biopsy Results: Significant Inflammation from esophagus to rectum



Patient Slide
Flattened mucosa with crypt elongation



Normal Comparison
Villi to Crypt ratio is 4:1

anemia, GERD, failure to thrive and mild eczema and required further consultation by hematology/oncology and gastroenterology services. Family history was significant for maternal hypothyroidism.

Physical

On physical exam, vital signs were stable. His weight was 3.6 kg (less than 3%), height was 54 cm (less than 5%), and the head circumference was 40 cm (50%). The infant appeared small, thin and tired. Examination of the head, ears, eyes, nose and throat revealed mucous membranes that were moist, the nasal mucosa was clear and fontanelles were flat. Cardiovascular exam and pulmonary exam were normal. The abdominal exam revealed a soft and benign abdomen with active bowel sounds and an umbilical hernia. His skin showed a dry scaly patch on the front scalp and bilaterally behind ears.

Laboratory

Laboratory evaluation was significant for metabolic acidosis with a capillary blood gas showing pH 7.28, pCO₂ 33, HCO₃ 15.3, BE: -10.5. The basic metabolic panel was significant for a CO₂ of 19.1, and CBC was normal with a white count of 15.2, hemoglobin of 11.2 and hematocrit of 33.9 and a platelet count of 494,000. An abdominal x-ray showed dilated loops of bowel. Pyloric ultrasound and upper GI performed one month prior to this admission were normal.

His initial working diagnosis was acute gastroenteritis. He was aggressively hydrated with IV fluids in addition to continuing home medicine regimen. Home feeds were continued. On day two, he continued to have emesis and diarrhea and on exam appeared pale and lethargic. He was found to be hypoglycemic with blood sugar of 34. CBG and renal panel confirmed metabolic acidosis with a CO₂ of 5.4. Abdominal film suggested a functional ileus. Insulin was stopped and he was bolused with normal saline and D10. Blood cultures were drawn and meropenem was started. After feeds were stopped and a nasogastric tube placed, he was transferred to the pediatric intensive care unit (PICU).

The patient improved from day two until day four. Pedialyte and pregestimil were restarted in two days with no emesis or excessive stool, and an abdominal ultrasound was normal. His diabetes was well controlled with decreased scheduled insulin. Meropenem was stopped after a negative septic workup. With improvement, he was transferred to a medical floor.

From day four until six, diarrhea and emesis worsened with advancing feeds and the patient developed pallor and abdominal distention. A repeat capillary blood gas revealed a metabolic acidosis with pH 7.195, pCO₂ 28.6, HCO₃ of 10.8, and BE -5.0. Hypoglycemia returned with sugars in the low 30's. He returned to the PICU and feeds were stopped. A nasogastric tube was placed and an insulin drip was started.

In the PICU, he initially was documented to have stools greater than 100 cc a day, which was difficult to measure because of its very liquid nature. Diarrhea resolved with NPO status as before, but would invariably resume with resumption of feeds. Octreotide was started on day 11, and the patient was able to tolerate Pedialyte and half strength neocate; however, when neocate full strength was offered, the diarrhea resumed. He resumed Pedialyte, but when challenged with reduced carbohydrate formula on day 13, diarrhea resumed.

Infection workup was unremarkable including cultures of the stools. His celiac and metabolic workup was normal. His immune workup was significant for a Coombs' positive anemia and an elevated IgE at 872. Eventually, antithyroglobulin antibodies were reported to be positive, and anti-enterocyte antibodies were also positive. T and B cell studies were normal and an ANA was normal.

An upper endoscopy and colonoscopy were performed. A biopsy demonstrated significant inflammation from esophagus to rectum with complete villous atrophy and crypt elongation and inflammatory infiltrates in the lamina propria (FIG 1).

Based on the clinical picture, the patient was suspected to have IPEX syndrome (Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked), a rare, lethal autoimmune disorder. IPEX was confirmed by genetic testing, which revealed an adenine to guanine point mutation in the P53 gene. Flow cytometry also revealed a decreased amount of P53 protein present in T cells.

His diarrhea resolved with oral tacrolimus and steroid therapy. He underwent bone marrow transplant on October 28, 2005. He is now greater than 100 days post-transplant with no evidence of acute rejection.

Discussion

IPEX (Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked) is a rare X-linked recessive syndrome that causes aggressive autoimmunity and early death. Clinically, patients usually present with symptoms shortly before birth or during the first three months, most commonly with enteropathy, neonatal diabetes and failure to thrive.^{1,2} Eczema, Coombs' positive anemia and hypothyroidism are less common symptoms. Asthma, ulcerative colitis and rheumatoid arthritis are rare, but seem to become more prevalent as patients survive longer. Mortality is greater than 90 percent with median age of death at 6 months, most commonly due to complications from diarrhea/malnutrition, diabetes and sepsis. The incidence of IPEX is thought to be extremely rare, with only 54 cases identified in the literature from a 2001 case review.¹

IPEX is definitively diagnosed by genetic sequencing signifying a mutation in the p53 gene; although both clinical presentation and family history are important. Other laboratory tests are suggestive but not definitive. Eosinophilia is common as well as elevated IgE levels. Autoantibodies are found in some cases but not in others. These include antibodies against thyroid, islet cells, insulin, GAD, enterocytes, ANA and red blood cells (positive Coombs'). T subset populations and CD4+/CD8+ populations are normal. GI endoscopy and biopsy often show absence of normal small mucosa and presence of inflammatory cells in the lamina propria and/or submucosa. Large bowel inflammation is not common.

Treatment of IPEX is extremely difficult and has included both chronic immunosuppression and bone marrow transplant. Immunosuppression usually consists of a regimen combining tacrolimus and steroids. It has been limited by ineffective long-term immunosuppression as autoimmune symptoms redevelop and progress as well as significant complications of treatment, such as renal toxicity and increased risk for sepsis. Recently,

CME QUESTIONS

9. Which of the following is NOT a symptom of IPEX?
- Hemolytic anemia
 - Diarrhea
 - Neonatal diabetes
 - Cataracts
 - Cachexia
10. How is the definitive diagnosis of IPEX made?
- Analyzing T and B cell subsets
 - MRI
 - Autoantibody analysis
 - Genetic sequencing
 - CD4+/CD25+ Flow cytometry
11. What is NOT a treatment for IPEX?
- Interferon-gamma
 - Bone marrow transplant
 - Tacrolimus
 - Prednisone
 - Sirolimus

sirolimus (rapamycin), an immunomodulator that represses both T and B cells has shown promise in achieving better remission.³ Bone marrow transplant is theoretically curative as the FOXP3 gene is only active in CD4+CD25+ regulatory T cells. Results have been mixed due to known risks of the procedure such as transplant rejection and sepsis as well as unforeseen risks such as hemophagocytic syndromes.

IPEX pathopathology is well-delineated because of a perfect model that naturally occurs in mice. "Scurfy mice" exhibit x-linked inheritance of scaly skin, cachexia, diarrhea, progressive anemia, sepsis and death by four weeks. These mice lack functional regulatory T cells, and it has been reported that they have a mutation in a gene termed FOXP3 that encodes a transcription factor that could repress cytokine production. It also was reported that scurfy mice also could be rescued from their disease with a single injection of normal T cells during the neonatal period. This proposed a solution for IPEX.

In humans, the P53 gene, found on chromosome 11, is only expressed on CD4+/CD25+ regulatory T cells. It encodes a transcription factor that is thought to play a role in control and maturation of regulatory T cells.⁴ The function of regulatory T cells is to inhibit T cell activation and differentiation into TH1 and TH2 cells. Regulatory T cells are less active during periods of infection, allowing T cells to proliferate. Conversely, they are more active when no infection is present, minimizing inappropriate immune responses. This model makes sense with the clinical presentation of IPEX. If regulatory T cells are not functional, T cells will activate and proliferate indiscriminately.⁵ This results in tremendous autoimmunity: neonatal diabetes develops as islet cells are destroyed as early as fetal life, intractable diarrhea develops as enterocytes are destroyed, Coombs' positive anemia develops as red blood cells are destroyed, cachexia develops as cytokine response is heightened and risk of infection paradoxically increases as the immune system is unable to effectively direct its response to pathogens.

Summary

IPEX is an autoimmune syndrome that presents most commonly with neonatal diabetes and enteropathy. The diagnosis is confirmed with genetic sequencing demonstrating mutations in the p53 gene. The syndrome is a result of regulatory T cell dysfunction allowing unchecked T cell expansion and differentiation ultimately resulting in tremendous autoimmunity. Current treatment options include chronic immunosuppression and bone marrow transplant but mortality remains extremely high. Neonatal diabetes and protracted neonatal diarrhea are rare disorders and require consideration of uncommon differentials.

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CT IMAGING FOR: APPENDICITIS



by **Barbara Wolfson, MD, FACR**

Dr. Wolfson is a radiologist at Dayton Children's. She completed a fellowship in pediatric radiology at St. Christopher's Hospital for Children in Philadelphia.

OBJECTIVES

After completing the article, the reader should:

1. Understand why CT is the modality of choice in diagnosing appendicitis.
2. Understand why GI contrast is necessary in children when performing a CT for appendicitis.
3. Understand the concern regarding the amount of radiation administered during CT examination in children.

Computed Tomography (CT) imaging has become the modality of choice to make the diagnosis of appendicitis when the clinical picture is uncertain¹. When the diagnosis is clear, no imaging is required and the patient is taken directly to surgery. Conventional wisdom states that a normal appendectomy rate of 20% is necessary to minimize the incidence of perforation²; however, the imaging community is diligently working to reduce both the normal appendectomy rate and the perforation rate. Different modalities have been used over the years to try to differentiate a normal appendix from an abnormal one, such as barium enema and ultrasound, but CT has proven to be the most accurate. In one recent report using CT selectively³, the normal appendectomy rate dropped to 3%. CT has been found to be more cost-effective than admission for observation or worse, missing appendicitis⁴. CT also has the capability of diagnosing other pathology such as pyelonephritis and inflammatory bowel disease.

The technique for performing CT for appendicitis varies from institution to institution. At some institutions no contrast is given because most adults have enough intraabdominal fat providing adequate contrast to allow the appendix to be seen; however, most children do not have sufficient intraabdominal fat (Fig 1), so gastrointestinal (GI) contrast must be given. Oral contrast may be used, but it can take several hours for the contrast to reach the right lower quadrant and can waste valuable time in the setting of acute appendicitis. At Dayton Children's, rectal contrast is used to help differentiate a normal appendix (Fig 2) from appendicitis (Fig 3). Intravenous (IV) contrast also is used because inflammation shows enhancement.

An important consideration when ordering a CT of the abdomen for appendicitis is the radiation dose administered to the patient. The increased use of CT has been reported to potentially increase the rate of expected malignancy in the general population⁵. This is statistical data but must be taken seriously when treating children. The Dayton Children's medical imaging department uses the least amount of radiation possible to obtain a diagnostic examination. We believe that children are always best served by dedicated pediatric professionals.



FIGURE 1. *Non-contrast CT: Coronal reconstruction of abdominal CT in a 3-year-old boy examined for possible renal calculi. The study was performed without GI or IV contrast. The appendix cannot be identified in the right lower quadrant.*

CME QUESTIONS

- 12.** True/False
The technique for performing CT of the abdomen in appendicitis is the same at all institutions.
- 13.** True/False
Radiation dose should be considered when ordering a CT examination on a child.

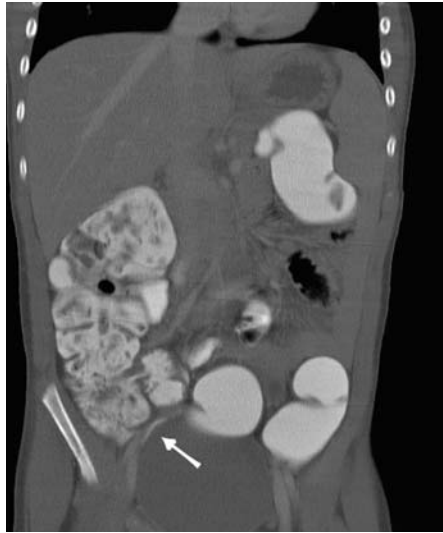


FIGURE 2. Normal Appendix:
Coronal reconstruction showing normal appendix (arrow) in a 5-year-old boy. Rectal and IV were administered.

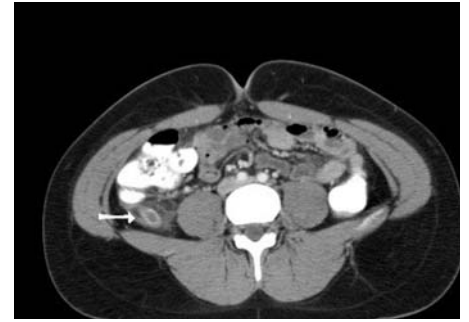


FIGURE 3. Acute Appendicitis:
CT axial image through the level of the cecum and appendix in a 13-year-old female. Rectal and IV contrast were administered. The appendix (arrow) is fluid-filled, does not fill with contrast and shows enhancement of the wall.

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ANSWER SHEET

PEDIATRIC FORUM,
VOLUME 17,
NUMBER 1

Physician accreditation statement and credit designation

Accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians. Wright State University (WSU) takes responsibility for the content, quality and scientific integrity of this CME activity. This educational activity is designated for a maximum of two hours in category 1 credit toward the American Medical Association Physician's Recognition Award. Each physician should claim only those hours of credit he or she spent on the activity.

Instructions

To obtain CME credit you must:

- Answer the questions from each article and complete this answer sheet.
- Complete the program evaluation located on reverse side.
- Return your completed answer sheet and program evaluation by mail or fax to:

Bev Comer, coordinator
Department of Continuing Medical Education
The Children's Medical Center of Dayton
One Children's Plaza
Dayton, OH 45404-1815

Fax: 937-641-5931

The answer sheet and program evaluation must be received by **June 30, 2007** for the credit to be awarded.

Upon completion of all requirements, Wright State University will issue a memorandum of credit to you for your permanent records.

Answers (Please circle the BEST answer.)

- | | | | | | |
|-----|------|-------|---|---|---|
| 1. | a | b | c | d | e |
| 2. | a | b | c | d | |
| 3. | a | b | c | d | e |
| 4. | a | b | c | d | |
| 5. | a | b | c | d | |
| 6. | a | b | c | d | |
| 7. | a | b | c | d | |
| 8. | a | b | c | d | |
| 9. | a | b | c | d | e |
| 10. | a | b | c | d | e |
| 11. | a | b | c | d | e |
| 12. | True | False | | | |
| 13. | True | False | | | |

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THANK YOU!

PROGRAM EVALUATION

PEDIATRIC FORUM,
VOLUME 17,
NUMBER 1

1. Did the material presented in this publication meet the mission to enhance health care delivery in our region through education based on the essentials and policies of the Accreditation Council for Continuing Medical Education? (Circle one response.)

Strongly agree Agree Neutral Disagree Strongly disagree

2. Did the material presented in this publication meet the educational objectives stated?

_____ Met the stated objectives

_____ Did not meet the stated objectives

3. Please rate the contents of this issue using the following scale:

1 = Poor, 2 = Fair, 3 = Good, 4 = Very good, 5 = Excellent

(Circle one response for each.)

	Poor			Excellent	
Timely, up-to-date?	1	2	3	4	5
Practical?	1	2	3	4	5
Relevant to your practice?	1	2	3	4	5

4. Please describe any changes you plan to make in your clinical practice based on the information presented in this program.

5. Are there any other topics you would like to have addressed in this publication?

_____ Yes

_____ No

If yes, please describe: _____

6. Any other comments/suggestions for future educational programs for health care providers? _____

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NEWS AND UPDATES

THE CHILDREN'S MEDICAL CENTER OF DAYTON



Laurence Kleiner, MD



*Springboro Testing Center
adds new services*

PICU and IV therapy recognized

Dayton Children's has been ranked first in a national safety collaborative to reduce infections associated with central venous catheters. The Child Health Corporation of America (CHCA) is coordinating the collaborative, which includes 29 children's hospitals from throughout the country. The collaborative began in April 2005. Before the start of the project, central venous catheter associated bloodstream infections tended to happen in pediatric intensive care unit patients every two to three months. During the past year, Dayton Children's has not had any bloodstream infections associated with the use of a central venous catheter in the pediatric intensive care unit. As a result of these outstanding results, Dayton Children's received a national award from the Child Health Corporation of America in April 2006.

Medical director of surgery appointment

Laurence Kleiner, MD, has been appointed medical director for surgery at Dayton Children's. We look forward to his leadership in continuing the tradition of providing excellent surgical services to our young patients. This is a newly created position that was recommended by consultants engaged to help us improve service and coordination in surgical services. Congratulations to Dr. Kleiner and we thank him for agreeing to take on this important responsibility.

Hyperbaric oxygen in cerebral palsy study

Wright State University Boonshoft School of Medicine Department of Pediatrics, Dayton Children's and Kettering Medical Center's Wound Healing and Hyperbaric Medicine Center are conducting a research study to evaluate the effects of hyperbaric oxygen and hyperbaric air treatments in children with spastic cerebral palsy. Eligible volunteers include children age 3 to 8 years old who have spastic cerebral palsy and who have never received hyperbaric treatments. Qualified volunteers may receive at no cost: neurological testing, hyperbaric treatments, physical examinations associated with this study, study-related medical care and will be closely monitored by a team of physicians, nurses, physical therapists and a psychologist. For more information, call research nurse coordinator Connie Bruns at 937-641-4279.

New referral tools available

The 2006 fax referral books and a new referral CD-ROM have been mailed to referring offices. The new referral CD-ROM is an electronic referral tool that includes specialty clinic and service information for most of Dayton Children's services, downloadable and savable referral forms, links to online forms and Dayton Children's website, driving directions and maps and central scheduling contact information. For more information on these tools, or to request additional copies, call marketing communications at 937-641-3618 or Ruthie Laux, physician liaison, at 937-641-3498.

New services added to Springboro Testing Center

Ultrasound, cardiac echocardiograms and EKGs are now available at the Springboro Testing Center by physician referral. Tests are performed by pediatric specialists at a convenient location for families south of Dayton. Call Melanie Hines at 937-641-5701 for more information.

New Pediatric Connection with Community Mercy Health Partners

Dayton Children's is pleased to announce a new Pediatric Connection with Community Mercy Health Partners (CMHP) in Springfield. This collaboration will begin with CMHP implementing pediatric asthma and bronchiolitis treatment protocols developed in collaboration with Dayton Children's. Pediatric Connection is an extension of a successful relationship between Dayton Children's neonatologists and Community Hospital's Birthing Center, enabling newborns born in the region to have neonatology services in Springfield.

NEWS AND UPDATES

Adolescent/Adult Congenital Heart Disease Clinic

Dayton Children's Cardiology began a monthly adult congenital heart disease clinic at Dayton Children's in January. The clinic's goal is to provide quality outpatient care to adults with unrepaired, palliated or repaired complex congenital heart disease. Call Joseph Ross, MD, at 937-641-3418 for more information.

GRAND ROUNDS ON DEMAND!

Grand rounds are now available on DVD or CD for your convenience. Dayton Children's now offers free Continuing Medical Education credits to you, at your convenience via your computer or DVD player. One grand rounds session will be recorded each month, featuring a variety of pediatric experts and topics. Each CME packet will include a test for one Category 1 CME credit.

To receive a FREE CME packet, complete the following information and return via fax to 937-641-3454 or e-mail a detailed request to eckertl@childrensdayton.org.

Indicate your interest below. Call 937-641-3618, fax the form to 937-641-3454 or mail to:

The Children's Medical Center
of Dayton
Marketing Communications
One Children's Plaza
Dayton, OH 45404-1815.

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**Please provide an e-mail address and fax number so we can provide you with notification when other sessions become available*

Please mark the session(s) you would like to receive:

Please mark your format preference: DVD CD-ROM

Avian Influenza — Thomas Herchline, MD, originally presented on 4/12/06 (expires 4/12/07)

Adolescent Behavior Seminar — Doug Teller, MD, originally presented on 3/29/06 (expires 3/29/07)

Adverse Events in Pediatric Transfusion — James Alexander, MD, originally presented on 4/26/06 (expires 4/26/07)

HIV Update 2006 — Jeffrey Weinstein, MD, originally presented on 1/11/06 (expires 1/11/07)

Immunizations Update — Sherman Alter, MD, originally presented on 2/8/06 (expires 2/8/07)

Neurosurgical management of children with spina bifida/myelomeningocele — Laurence Kleiner, MD, originally presented on 3/11/06 (expires 3/11/07)

Yes No I would be interested in earning online CMEs.

Please deliver to current resident

Street Directions

FROM THE NORTH:

I-75 south, Exit 54C to Rt. 4; stay left when exiting I-75; Rt. 4 north to Valley St./Troy St. exit. Go through first stop sign at bottom of exit ramp. Valley Street is the next stop sign. Turn left.

FROM THE SOUTH:

I-75 north, Exit 54C to Rt. 4; Rt. 4 north to the Valley St./Troy St. exit. Go through first stop sign at bottom of exit ramp. Valley Street is the next stop sign. Turn left.

Or I-675 north, Exit 13 to Rt. 35; west on Rt. 35 to the Keowee St. exit; right on Keowee to Valley St.; right on Valley St.

FROM THE EAST:

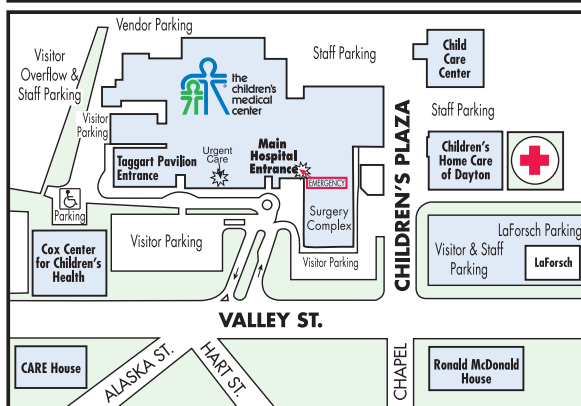
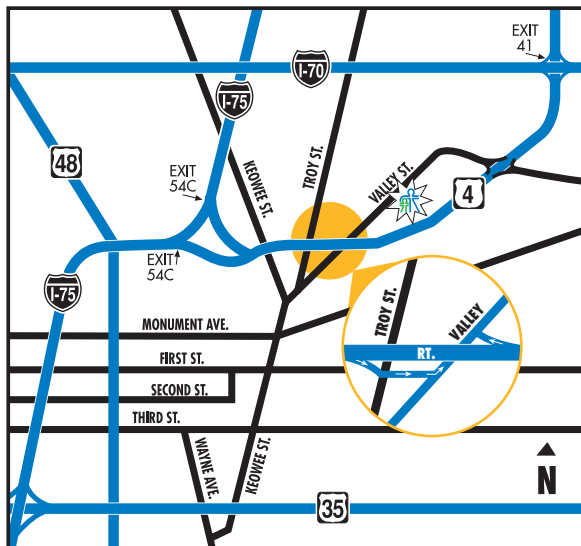
Rt. 35 west to the Keowee St. exit; Keowee St. north to Valley St.; right on Valley St. From I-70 exit 41, take Route 4 south to Stanley Ave./Findlay St. exit. Turn right at the bottom of exit, then left at the first light on Stanley Ave. This is Valley St.

FROM THE WEST:

Third St. east to Keowee St.; left on Keowee St. to Valley St.; right on Valley St.

For Your Information

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