

The Child's Doctor

Journal of Children's Memorial Hospital, Chicago



In This Issue:

- Earn 2 AMA PRA Category 1 Credits™ Free
- ACL Injuries in Young Athletes
- Preventing Vitamin D Deficiency
- Unraveling the Mystery of SIDS
- Pediatric Obesity
- Dermatology


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On the cover: Sports medicine physician Rebecca Carl, MD, with Caroline Dunphy, patient and participant in the Knee Injury Prevention Program (KIPP)

Photography by Andrew Campbell

The Child's Doctor

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[2] CME: Anterior Cruciate Ligament Injuries in Young Athletes

Rebecca L. Carl, MD, attending physician, Institute for Sports Medicine

Educational Objectives: Describe the prevalence of anterior cruciate ligament (ACL) injuries in young athletes; conduct diagnostic assessment and consider management options; discuss prevention of ACL injuries with young athletes

[7] CME: Preventing Vitamin D Deficiency in Pediatrics

Farah N. Ali, MD, attending physician, Kidney Diseases

Educational Objectives: Explain rationale behind recent AAP guidelines to double vitamin D intake from infancy through adolescence, compared to previous recommendations; discuss classical actions of vitamin D and its newly recognized functions; describe risk factors for vitamin D deficiency that might call for higher doses of vitamin D to prevent deficiency

[11] CME: Emotional and Behavioral Aspects of Pediatric Obesity

Kelly Walker Lowry, PhD, medical psychologist, Child and Adolescent Psychiatry

Educational Objectives: Describe common psychiatric and psychological comorbidities in overweight or obese youth; identify common symptoms of depression, anxiety, disordered eating behaviors, poor self-esteem or body dissatisfaction, and peer teasing; recognize when to refer a child or family to a mental health specialist for further evaluation or treatment

[15] CME: Unraveling the Mystery of Sudden Infant Death Syndrome (SIDS)

Debra E. Weese-Mayer, MD, medical director, Center for Autonomic Medicine in Pediatrics (CAMP)

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Aimee C. Smidt, MD, fellow, Pediatric Dermatology
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Anterior Cruciate Ligament Injuries in Young Athletes

REBECCA L. CARL, MD

Over the last 2 decades, the medical community has become increasingly aware that anterior cruciate ligament (ACL) injuries affect not just adults, but children and adolescents as well. Many sports physicians who take care of children are seeing a rise in the number of young patients, especially female athletes, who present with ACL tears.¹ There are several explanations for this phenomenon. Advances in medical imaging and increasing awareness that skeletally immature patients can tear their ACLs have improved the rate of diagnosing these injuries. Additionally, greater numbers of children are playing sports such as soccer and basketball year-round. The passage of Title IX in 1972 has dramatically increased the numbers of girls and young women playing sports at every level.² This article will review the diagnostic assessment and management approaches to ACL injuries, as well as discuss the growing focus on effective prevention of these injuries in young athletes.

Educational Objectives

At the conclusion of this activity, participants will be able to:

- Describe the prevalence of anterior cruciate ligament (ACL) injuries in young athletes
- Conduct diagnostic assessment and consider management options
- Discuss prevention of ACL injuries with young athletes

The ACL is 1 of 4 major ligaments that provide stability to the knee. The word “cruciate” is derived from the Latin word for cross; the anterior and posterior cruciate ligaments cross each other in the center of the knee. (See illustration of ACL anatomy in Figure 1). The main function of the ACL is to prevent the tibia from sliding forward relative to the femur; this ligament also prevents excessive extension, varus and valgus positioning at the knee joint, and tibial rotation.^{3,4} An intact ACL protects the menisci, the cartilage shock absorbers of the knee, against shearing forces with twisting and pivoting motions.

Who is at higher risk?

Although there have been no large-scale population studies in children, epidemiologic studies have demonstrated that ACL tears are common in adults. An examination of patient records for the national health care system in Norway revealed that 85 reconstructions are performed there per 100,000 individuals in the 16-39-year-old age group.⁵ In college athletics, participants in men’s football and women’s gymnastics, basketball and soccer have the highest rates of ACL injury.

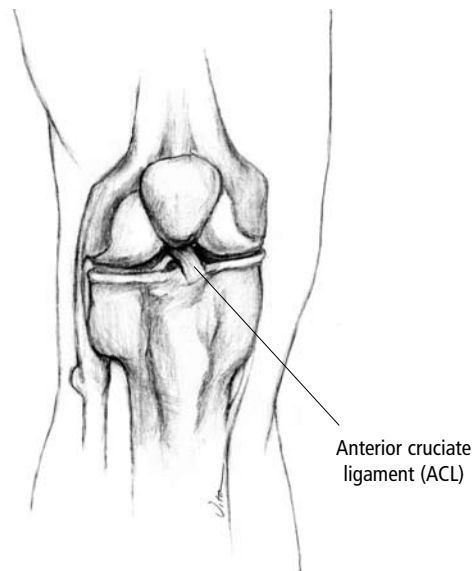


FIGURE 1: *Front of right knee*

Studies have consistently shown that female athletes, particularly those who participate in sports involving twisting and pivoting, have significantly more non-contact ACL tears than males in similar sports. An examination of records from the National College Athletic Association (NCAA) found that female soccer



Knee Injury Prevention Program

To reduce her risk of ACL injuries, the 15-year-old athlete Caroline Dunphy (above) participates in the Knee Injury Prevention Program (KIPP), a preseason neuromuscular training program specifically designed for female athletes between 12 and 18 years of age. Children's Memorial Institute for Sports Medicine offers KIPP preseason training to individual athletes, and also trains coaches of female athletic teams how to implement a 15-minute KIPP warm-up into their regular practices.

The Institute for Sports Medicine's Medical Director Cynthia LaBella, MD, recently won the "Best Overall Research" award at the American Medical Society for Sports Medicine 2009 annual conference, where she presented her research results showing that the KIPP warm-up reduced ACL injuries by 80% among female soccer and basketball athletes in Chicago Public High Schools.

For more information on KIPP, visit childrensmemorial.org/sports or call 773.327.1201.

**At the age of 14 years,
girls have 5 times
higher rates of ACL tears
than boys.**

players have more than twice the risk and female basketball players have 4 times the risk of non-contact ACL tears when compared to their male counterparts.⁶ ACL disruptions are uncommon in young children; risk increases significantly at age 12-13 years in girls and age 14-15 years in boys. At the age of 14 years, girls have 5 times higher rates of ACL tears than boys.⁷

Diagnostic assessment

The diagnosis of an ACL tear can generally be made with a good history and physical

examination. Clinical history can be very useful in discerning the pathology present after an acute knee injury. O'Donoghue described ACL injury as being part of an "unhappy triad"; he provided the classic description of a player who is hit in the lower leg from the lateral side and sustains a medial meniscal injury, as well as ACL and medial collateral ligament (MCL) tears.⁸ However, the majority of ACL tears are non-contact injuries; athletes may recall the injury occurring with a pivot or twist, landing from a jump, or a sudden deceleration.^{9,10} Over 70% of

In patients with a substantial amount of growth remaining, many physicians recommend non-operative treatment with physical therapy, bracing and activity modification until the patient approaches skeletal maturity.



FIGURE 2: Lachman maneuver: With the knee flexed slightly, the examiner stabilizes the femur and attempts to translate the tibia anteriorly. In the presence of an ACL tear, excessive motion/translation is present and the stopping point feels soft. The contralateral leg can generally be used as a comparison.

affected patients report hearing a “pop.”¹⁰ Many patients are able to bear weight following an ACL disruption. Development of hemarthrosis occurs rapidly; athletes often note that significant swelling appears within several hours of their injury.

Several weeks after their injury, young athletes are often relatively asymptomatic with activities of daily living. A sense of instability or feeling that the knee is giving way with twisting or lateral motion is the hallmark of ACL insufficiency. Clinicians should ask young patients about their recent growth and pubertal stage (including age of menarche for females), as skeletal maturity influences the treatment of these injuries.

In the acute phase following injury, practitioners can often detect swelling and limited range-of-motion during the physical examination.

Many patients note resolution of effusion and achieve full motion within 1-2 weeks of their injury. The Lachman maneuver (Figure 2) assesses for anterior translation of the tibia; this technique has 85% sensitivity for detecting ACL insufficiency. The pivot shift maneuver is highly specific for ACL injury, but is technically more difficult to perform and has a low sensitivity. Both tests are more accurate when used with a patient who is able to relax the muscles around the knee.¹¹ Physical examination should also include evaluation for associated injuries, including fractures and meniscal tears, and determination of Tanner stage in the skeletally immature patient.

Imaging is generally used for confirmation of physical findings and to determine the presence of associated injuries. Plain radiographs may detect associated injuries, such as tibial spine avulsion fractures; they can also aid in determining skeletal maturity. In addition to confirming the diagnosis of an ACL tear, magnetic resonance imaging (MRI) helps evaluate for the presence of meniscal and articular cartilage lesions. (Figure 3 shows a sagittal MR image illustrating an ACL injury). Meniscal injuries are commonly associated with ACL tears; a study of adults found meniscal tears in 73% of patients.¹² Millett et. al. found associated injuries, including lateral and medial meniscal tears, MCL ligament injuries and a femur fracture, in 66% of 10-14-year-old patients undergoing surgery for ACL reconstruction.¹³ MRI will detect bone bruises in over 70% of patients who undergo imaging within 6 weeks of their injury, but this finding is generally of little clinical significance.¹⁴

Management approaches

In the acute phase, athletes with ACL tears can be managed with “RICE” – rest, ice, compression and elevation – with progression to range-of-motion exercises and quadriceps and core abdominal/trunk strengthening. Surgical reconstruction is uniformly recommended for

skeletally mature athletes. The ACL cannot be directly repaired; it must be replaced with a graft. A variety of surgical techniques and graft choices have been employed with good results.

Management of the skeletally immature athlete with an ACL tear remains controversial. Surgical techniques that place the graft in an anatomic position require drilling through the physis; this carries a risk of growth arrest with possible limb-length inequality and angular deformity. Certain drilling techniques appear to be quite safe, but given the potentially devastating consequences, sports physicians often recommend against surgeries that involve a trans-physeal approach for boys younger than 14 years and girls younger than 13 years. There are several reconstruction procedures that avoid the growth plate; however, they place the graft in a less anatomic position and this may result in the need for future revision surgery.

In patients with a substantial amount of growth remaining, many physicians recommend non-operative treatment with physical therapy, bracing and activity modification until the patient approaches skeletal maturity. Graf found that patients with ACL insufficiency treated non-operatively with bracing and physical therapy had a high risk of sustaining a subsequent meniscal tear.¹⁵ Another group imposed more stringent activity restrictions along with non-operative therapy and did not note a significant rate of ensuing meniscal injuries.¹⁶ Adults appear to do very well with activity modification and bracing; however, the studies involving children and adolescents are small and many clinicians are concerned that children will be less compliant with restrictions to participation in athletics.¹⁷

Long-term follow-up of athletes who have sustained ACL tears has consistently shown an increased risk of osteoarthritis. This is especially true for patients with associated meniscus and articular cartilage lesions. However, even individuals who have undergone surgical reconstruction for isolated ACL tears appear to be at increased risk for degenerative joint disease.¹⁸

Prevention programs

Given the concerns in managing ACL injuries in skeletally immature athletes, prevention has been an area of active research over the last decade. Most ACL prevention programs have focused on female athletes in an attempt to mitigate their significantly increased risk of injury. Hewett, et al. noted differences between female and male athletes in hamstring strength and mechanics when landing from a jump.¹⁹ Female athletes tend to land in an upright position with increased dynamic internal rotation of the knees and decreased hip and knee flexion. Hewett's



FIGURE 3: *Sagittal MR image of a complete ACL tear*

group instructed coaches and trainers on how to institute a neuromuscular training program emphasizing plyometrics, strength and flexibility. They found that untrained athletes had a 3.6 times higher rate of injury compared to trained athletes.²⁰

Several centers have subsequently instituted successful neuromuscular training programs. Cynthia LaBella, MD, medical director of Children's Memorial Hospital's Institute for Sports Medicine, has established and continues to expand the Knee Injury Prevention Program (KIPP) in Chicago Public High Schools (CPS). In one study she found that female adolescent athletes who participated in KIPP during their preseason training reported lower rates of sport-related knee pain and improved self-rated athletic performance post-KIPP vs. pre-KIPP.²¹ Data from the first year of implementing KIPP at 46 Chicago public high schools revealed a 66% reduction in knee ligament injuries and an 80% reduction in ACL tears among participating vs. non-participating female soccer and basketball athletes (written communication, March 2009; data presented at the American Medical Society for Sports Medicine, April 2009).

Conclusion

ACL injuries are an increasing concern for young athletes, especially girls, and their families. Care of the skeletally immature patient with an acute knee injury requires a multidisciplinary team of physicians, physical therapists and orthotists who are familiar with the particular needs of this population. Because management of ACL tears in young patients involves unique challenges, there is a greater impetus to reduce injuries in this population. Research shows that participation in an appropriate neuromuscular training program can significantly reduce the risk of ACL tears in female athletes.

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Preventing Vitamin D Deficiency in Pediatrics

FARAH N. ALI, MD

Vitamin D deficiency is now increasingly recognized throughout the United States as a problem that may affect numerous patient populations. Even more concerning to general practitioners has been the growing prevalence of this condition in otherwise healthy children. Contributing to widespread vitamin D deficiency are few naturally available dietary sources and insufficient sun exposure that is exacerbated by the need to use sunscreen products to prevent skin cancer. Preventing deficiency has gained considerable attention, especially in light of the emerging evidence that vitamin D has other important functions, in addition to optimizing bone and mineral metabolism. Addressing these evolving issues, the American Academy of Pediatrics (AAP) in recently updated guidelines has doubled the vitamin D intake recommended for infants, children and adolescents.¹ Pediatricians are now faced with a critical role in promoting adequate vitamin D intake in their patients and identifying children at higher risk for deficiency who may require more vitamin D to maintain health.

Prevalence and definition of vitamin D deficiency

Symptoms of vitamin D deficiency may be vague in infants, and many children and adolescents are asymptomatic. However, severe deficiency of this nutrient in children may lead to rickets and at times can present with seizures related to hypocalcemia.

Vitamin D deficiency is determined by measuring serum 25-hydroxyvitamin D or 25(OH)D levels. While controversy remains over the definition of optimal levels of 25(OH)D, one possible index of normalcy relates to prevention of secondary hyperparathyroidism. Based on this feature, insufficiency may occur at levels of 25(OH)D < 32 ng/mL, since elevation of parathyroid hormone (PTH) was noted in adults once levels fell below this threshold value.² This relationship was also demonstrated in healthy adolescents.³ The AAP recommends on the basis of available evidence, that serum 25(OH)D concentrations in infants and

children should be at least 20 ng/mL (50 nmol/L).¹ Previously, vitamin D deficiency was considered to occur at levels < 11 ng/mL.

Although changing definitions of deficiency complicate estimates of prevalence, studies indicate that too many individuals lack enough vitamin D for overall health. One recent publication has described the deficiency of vitamin D as a pandemic.⁴ A new meta-analysis of cross-sectional data from 394 studies, including pediatric data, showed widespread global vitamin D deficiency; the mean reported 25(OH)D level in children younger than 15 years of age was 14.8 ng/mL (37 nmol/L).⁵

In a study of more than 1,000 children, our group at Children's Memorial Hospital has uncovered that up to 75% of patients seen in the kidney disease practices were vitamin D deficient during a decade of study, with deficiency defined as 25(OH)D < 15 ng/mL. In addition, we found an increasing prevalence of nutritional vitamin D deficiency during that decade.⁶

Educational Objectives

At the conclusion of this activity, participants will be able to:

- Explain rationale behind recent AAP guidelines to double vitamin D intake from infancy through adolescence, compared to previous recommendations
- Discuss classical actions of vitamin D and its newly recognized functions
- Describe risk factors for vitamin D deficiency that might call for higher doses of vitamin D to prevent deficiency

Any exclusively breast-fed infant or any infant drinking less than 1 liter of vitamin D-fortified formula per day will require additional supplementation to get at least 400 IU of vitamin D each day.

AAP guidelines

To improve prevention of vitamin D deficiency given new considerations about the levels needed to maintain health, the AAP has published updated guidelines recommending that a minimal daily intake of 400 IU of vitamin D begin soon after birth and continue throughout adolescence.¹ This means that any exclusively breast-fed infant or any infant drinking less than 1 liter of vitamin D-fortified formula per day will require additional supplementation.

The new minimum daily intake doubles the amount in the AAP's previous recommendations, which advised 200 IU of vitamin D per day beginning in the first 2 months of life, to continue through adolescence. The earlier minimum intake was thought to prevent physical signs of vitamin D deficiency and maintain levels of 25(OH)D \geq 11 ng/mL. However, newer information examining biomarkers linked to vitamin D deficiency in adults (eg, PTH, bone mineralization, insulin resistance, calcium absorption) has raised concerns that this minimum intake is not sufficient, even for infants and children, and the safety of 400 IU per day has long been established.

Actions of Vitamin D

Vitamin D (cholecalciferol) is synthesized from its precursor, 7-dehydrocholesterol, in the skin via isomerization due to the effects of UVB exposure from the sun. Cholecalciferol then undergoes 2 subsequent hydroxylations: the first takes place in the liver at the carbon-25 position through the actions of 25-hydroxylase and the second occurs in the proximal tubule of the kidney, where 25(OH) vitamin D is further modified by a 1- α -hydroxylase, to form 1,25(OH)₂ vitamin D.

Vitamin D is most commonly recognized as being important for its traditional role in bone and mineral metabolism. 1,25(OH)₂ vitamin D is the major regulator for intestinal calcium and phosphorus absorption and has vital actions in maintaining serum calcium and phosphorus levels. It leads to increased renal

reabsorption of calcium and phosphorus and increased osteoclast activation in the bone. Ultimately, it is vitamin D adequacy that guarantees optimal skeletal mineralization, through these classic endocrine actions. In otherwise healthy children, severe deficiency of vitamin D leads to the classical findings of rickets, and under-mineralization of the skeleton; in adults the correlate is osteomalacia.

Aside from these classical aspects of vitamin D metabolism, there is mounting literature documenting numerous non-classical or non-endocrine actions of vitamin D as well. Vitamin D is involved in the regulation of the immune system and autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, and type 1 diabetes.⁷ It is implicated in control of cancer cell growth. Solar UVB radiation and thus vitamin D has been associated with reduced risk of multiple cancers, including breast, colon, ovary, prostate, and non-Hodgkin lymphoma.⁸ Vitamin D is also involved in regulating blood pressure through renin and deficiency may be related to cardiovascular diseases, such as hypertension and coronary heart disease.^{4,9,10}

Increased risk for vitamin D deficiency

Impaired synthesis and inadequate intake of vitamin D are major risk factors for vitamin D deficiency. Insufficient dietary intake has now been addressed by the new AAP guidelines. This is extremely important as there are very few naturally occurring dietary sources of vitamin D. The National Institutes of Health report cod liver oil, salmon, mackerel, sardines, beef liver, and egg yolk as providing significant levels of vitamin D. Fortified dietary sources of vitamin D may include milk, margarine, pudding, and dry cereal.

Inadequate sun exposure. Another risk factor for vitamin D deficiency is inadequate sun exposure. UV ray exposure that is necessary for synthesis of cholecalciferol in the skin may be affected by season, latitude, time of day, cloud cover, and smog. For example, in more northern latitude sites such as Chicago, there

is significantly lower vitamin D-producing UV radiance than at lower latitude sites; in fact at times the winter solar noon irradiance at lower latitude locations exceeds the summer values recorded in Chicago.¹¹ North of Atlanta (latitude 33°), the average amount of sunlight is insufficient to produce significant vitamin D synthesis from November through February. In addition, the use of sunscreens to reduce the risk of many skin cancers may be a factor, as sunscreens with SPF 8 or greater will block UV rays that produce vitamin D.

Darker skin pigment. It is also likely that individuals with darker skin pigmentation are at higher risk for vitamin D deficiency than their Caucasian counterparts. This may be due to the fact that an increased content of melanin in the skin may decrease vitamin D production.¹² Studies have confirmed that this is a problem that affects healthy children and adolescents, especially those with darkly pigmented skin.¹³⁻¹⁵

Decreased gastrointestinal absorption. Patients at higher risk for vitamin D deficiency may include children with gastrectomy, celiac disease, malabsorptive states, history of extensive bowel surgery, inflammatory bowel disease, and pancreatic insufficiency, including patients with cystic fibrosis.

Liver disease. Patients with liver disease are also at increased risk for vitamin D deficiency. As 25-hydroxylation normally occurs in the liver, this conversion can be impaired with severe liver disease.

Medications. Drugs that increase cytochrome P-450 enzyme activity, such as phenobarbital, carbamazepine, phenytoin, isoniazid, rifampin, and theophylline, increase 25-hydroxylation, but also increase catabolism of 25(OH)D and 1,25(OH)₂D to inactive metabolites. Children using these medications are at higher risk for vitamin D deficiency.

Kidney disease. It is well-documented that patients with kidney disease are at increased risk for vitamin D deficiency as well. The proximal

tubule is the site of 1,25(OH)₂ vitamin D production. It has been shown that in adults, progressive loss of kidney function defined by loss of estimated glomerular filtration rate leads to lower serum levels of 1,25(OH)₂ vitamin D and eventual secondary hyperparathyroidism.¹⁶ This is a multifactorial process involving low 1,25(OH)₂ vitamin D production, loss of the enzyme 1- α -hydroxylase, and hyperphosphatemia that occurs with reduced kidney function and serves as an additional negative stimulus.

Genetic disorders. A few genetic disorders involve abnormalities in vitamin D metabolism. Vitamin D-dependent rickets is an autosomal recessive disorder with hypocalcemia, hypophosphatemia, high parathyroid hormone and alkaline phosphatase concentrations, in addition to bony abnormalities. It is caused by inability to produce 1,25(OH)₂ vitamin D due to inactivation mutations in the 1-hydroxylase gene. Vitamin D-resistant rickets is associated with end-organ resistance to 1,25(OH)₂ vitamin D, most often due to mutations in the gene encoding the vitamin D receptor. Clinical findings are similar to those in vitamin D-dependent rickets except that serum 1,25(OH)₂ vitamin D concentrations are high, as opposed to the low levels seen in the former condition.

Prevention and treatment

The minimum recommended daily intake to prevent rickets and vitamin D deficiency in otherwise healthy infants, children, and adolescents is now 400 IU. Dietary sources may be included in this daily intake for each child, but this requires careful dietary assessment by the primary pediatrician. Liquid vitamins and vitamin D preparations available in the United States generally supply 400 IU per day.

Children with increased risk for vitamin D deficiency, such as patients with chronic fat malabsorption or receiving anti-seizure medications as outlined above, may require serum 25(OH)D status to be determined to ensure sufficiency. These patients may require

Children using these medications are at higher risk for vitamin D deficiency – phenobarbital, carbamazepine, phenytoin, isoniazid, rifampin, and theophylline.

Children with increased risk for vitamin D deficiency may require serum 25(OH)D status to be determined to ensure sufficiency, larger doses to reach target levels, and repeat testing at 3-month intervals to ensure normalization of the 25(OH)D level.

larger doses to reach target levels, and repeat testing at 3-month intervals would be indicated to ensure normalization of the 25(OH)D level.

Conclusion

The widespread prevalence of vitamin D deficiency necessitates attention to careful dietary assessment of intake and early initiation of multivitamin supplementation in patients who need it. If additional risk factors are found, it may be prudent to assess vitamin D status biochemically.

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Emotional and Behavioral Aspects of Pediatric Obesity

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Children and adolescents who are overweight or obese are at increased risk for certain psychiatric disorders and impaired psychological functioning. Community practitioners are often the first (or only) point of evaluation and intervention for these youth. Being able to recognize common symptoms of impaired emotional or behavioral functioning is essential to developing appropriate treatment plans and referrals when necessary.

Definition and epidemiology

Childhood overweight and obesity constitute a major public epidemic affecting up to 32% of youth 6-17 years old in the United States, with even higher incidence in certain ethnic minorities and families with lower socioeconomic resources.¹ In children and adolescents, obesity is frequently diagnosed by calculating body mass index (BMI = weight in kg/height in m²) and plotting the score on a gender and age specific growth chart. Youth with BMI scores between the 85th and 95th percentiles for gender and age are considered overweight, whereas youth with BMI scores at or above the 95th percentile are considered obese.²

Overweight or obese youth are at increased risk for a multitude of medical comorbidities affecting almost every major body system. Certain psychiatric and psychological disorders are also more common in overweight or obese youth (see Table 1).³ Recent expert committee guidelines for the prevention, evaluation, and treatment of child and adolescent overweight and obesity recommend screening for specific psychiatric concerns and intervening at the family level with a focus on behavioral changes.² Thus, familiarity with common emotional and behavioral risk factors and presentations in overweight and obese youth is essential to provide a comprehensive evaluation and treatment plan.

Depression and anxiety

Children and adolescents who are overweight or obese have increased rates of depression and depressive symptoms. Research suggests that the association between excess weight and depressive symptoms may be bi-directional, where the presence of one condition may increase the risk for the other condition. Furthermore, the presence of depression will likely impede clinical efforts to promote healthier eating and physical activity in patients.

Symptoms of depression in overweight youth may include negative affect or irritability. Other symptoms include anhedonia, or decreased interest in previously enjoyable activities, significant increases or decreases in sleep, a decline in school performance, psychomotor retardation, less engagement with peers, or rapid weight gain in the absence of other medical causes. These symptoms can leave youth trapped in a cycle that only perpetuates increased weight gain and negative affect. Symptoms of depression can be assessed through clinical interview or the use of brief self-report screening instruments such as the Children's Depression Inventory (CDI).⁴

Overweight or obese youth may also experience anxiety. Symptoms of anxiety may present around eating, physical activity, or in social settings. Anxiety around food consumption should serve as a red flag to assess eating behaviors in more depth (see pages 12-13).

Educational Objectives

At the conclusion of this activity, participants will be able to:

- Describe common psychiatric and psychological comorbidities in overweight or obese youth
- Identify common symptoms of depression, anxiety, disordered eating behaviors, poor self-esteem or body dissatisfaction, and peer teasing
- Recognize when to refer a child or family to a mental health specialist for further evaluation or treatment

Binge eating and other disordered eating patterns are important to assess because they may directly contribute to overweight and addressing these behaviors will directly affect weight management goals.

Table 1

COMMON PSYCHIATRIC COMORBIDITIES AND SYMPTOMS

<p>Depression</p> <ul style="list-style-type: none"> • Anhedonia (loss of pleasure/interest in previously enjoyable activities) • Psychomotor retardation and/or fatigue • Limited social interactions • Recent rapid weight gain • Decline in academic performance <p>Anxiety</p> <ul style="list-style-type: none"> • Anxiety around eating • Worries regarding weight and body size • Use of food to cope with anxiety • Anxiety in social settings 	<p>Eating Disordered Behaviors</p> <ul style="list-style-type: none"> • Loss of control when eating • Use of diet pills, laxatives, purging, excessive exercise or tobacco to control weight • Binge eating • “Crash dieting” • Eating in secret • Skipping meals <p>Impaired Family Functioning</p> <ul style="list-style-type: none"> • Limited level of concern for youth weight status • Parent overweight or obesity • Limited parent and child readiness to make behavioral changes • Limited parent ability to manage child behavior 	<p>Poor Psychological Adjustment</p> <ul style="list-style-type: none"> • Poor self-esteem • Body dissatisfaction • Peer victimization (reports of teasing and/or bullying behaviors) • Limited peer relationships • Feeling stigmatized due to weight • Poor coping skills, particularly use of food-based coping
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(Adapted from Lowry, in press.³)

Concerns about body size or past experiences of teasing may lead to avoidance of social activities. Avoidance may be overt and clear (eg, “I don’t want to go!”) or more subtle. Somatic complaints such as headache and stomachache at the time of the anxiety-inducing activities can be common in anxious youth. Symptoms of panic or anxiety may include racing heart rate, sweaty palms, and concerns for health. Organic causes for physical symptoms should always be assessed in conjunction with evaluation of triggering events, common settings or timing of symptoms, and consequences of the complaints. Symptoms of anxiety can be assessed through clinical interview or the use of brief self-report screening instruments such as the Screen for Child Anxiety Related Emotional Disorders (SCARED).⁵

Eating-disordered behaviors

Eating-disordered behaviors are also more common in overweight youth. Binge eating has been reported at increased rates and adolescents appear to be particularly vulnerable. Binge eating is characterized by eating more food in a distinct period of time than most people would eat in the same time frame and environment and a feeling of lack of control over eating during the experience.⁶ Binge eating may or may not be accompanied with inappropriate compensatory activities such as purging. The use of laxatives, diuretics, “crash dieting,” or excessive exercise should also be assessed.

Other common eating-disordered behaviors may include eating in secret, feeling that it is difficult to stop eating certain foods, or skipping meals. Use of over-the-counter diet supplements should

be carefully monitored to prevent inappropriate use or abuse. Binge eating and other disordered eating patterns are important to assess because they may directly contribute to overweight and addressing these behaviors will directly affect weight management goals. Any of these behaviors could serve as red flags to clinicians to assess further or refer the patient to a nutritionist and mental health specialist for evaluation and treatment. The Children's Eating Attitudes Test (ChEAT) is a brief patient-report questionnaire that could assist in screening.⁷

Poor self-esteem and body dissatisfaction

Self-esteem and body dissatisfaction (or poor body image) may be lower in overweight or obese youth. Self-esteem refers to an overall perception of self-worth, whereas body dissatisfaction refers to negative perceptions about physical appearance. Self-esteem is an important construct to consider in children because low self-esteem has been linked with behavioral disorders and emotional concerns, whereas improvements in self-esteem have been linked with improvements in other behavioral problems. Furthermore, self-esteem rates in adolescence may persist throughout adulthood.

The data on rates of self-esteem for overweight or obese youth is mixed, but certain factors appear to increase the risk for lower rates. Body dissatisfaction appears to be a major component of self-esteem, particularly for adolescents, females, and youth who place a higher value on identification with cultural standards for beauty and slimness. Individuals who are teased about their weight are also more likely to have lower rates of self-esteem. Signs of poor self-esteem or body dissatisfaction may include lack of confidence, shame about body shape or size, or desire to keep the body hidden or covered at all times (eg, difficulty with changing clothes in gym class). Self-esteem and body dissatisfaction can be assessed by asking open-ended non-judgmental questions about a child's or adolescent's perceptions of self (eg, "How do you feel about yourself?" or "Do you wish that you or your body were different?"). Participation in activities of interest to the child that allows him or her to feel a sense of confidence or success may help improve self-esteem. Clinical intervention efforts should focus on healthier eating and physical activity behaviors, not weight, to promote a sense of body health, not body size.

Peer victimization

Despite the increasing prevalence of obesity, negative stigma towards obesity has not normalized, but intensified. Although a mild degree of teasing may be normative for all children,

overweight or obese youth are more likely to be teased by their peers, experience more severe forms of teasing, and may be vulnerable to the negative experiences. Experiences of peer victimization may also increase the likelihood of a child becoming socially isolative or anxious in social settings. Signs that a child is being victimized by peers may include a sudden lack of interest in school, a preference for isolative activities, or attempts to avoid peer activities. At-risk children and adolescents may have difficulty making or sustaining friendships or have unrealistic beliefs that weight loss alone will improve peer relationships.

One way to assess the rate and intensity of teasing of patients is to query children and/or parents whether they think the child is teased more often than other same aged children. Parents can discuss any concerns with a teacher or other school personnel who are familiar with their child and the school social environment. Although individual interventions on behalf of a specific student can be beneficial, parents should be encouraged to speak with school personnel about classroom or school-wide policies to decrease bullying. This will prevent the child from feeling targeted or singled out, which may lead him or her to be less likely to report future negative experiences.

Family functioning

Less than 10% of all current cases of youth obesity are thought to be caused by medical or genetic conditions alone. The combination of genetic-environmental or environmental influences on child weight and health are significant and many parents of overweight or obese children may also be overweight. Youth and young children in particular may have little control over food purchasing decisions or physical activity opportunities. Therefore, successful interventions to promote healthier lifestyles will require a family-based approach. Family members may be successful at choosing small meaningful goals for behavior (eg, have 1 additional fruit or vegetable each day, be active for 30 minutes for 2 days next week). However, not all family members may be at the same level for desire to change current behaviors and habits.

The concept of motivation to change, or readiness to change, is a popular term to describe the assessment and attempts to tailor interventions based on an individual's willingness to make changes in a specific behavior. The concept is straightforward, but putting it into clinical practice with children and parents can be challenging, particularly if family members differ in their desire to make changes. Often a parent is ready to make changes, but a child may be less motivated. This may be reflective of an overall pattern of parent difficulty with child behavior

management or an isolated problem. General suggestions on behavior management or referral to a mental health specialist may be helpful if parents report difficulty implementing changes in child behavior.

If both the parent and child are not yet ready to make changes, health education and motivational interviewing approaches may be more beneficial until the family is ready to commit to a more intensive treatment plan. Numerous studies have shown that many parents of overweight children do not recognize that their child is overweight. At this stage, sensitive and nonjudgmental education about the child's weight risk may be sufficient until the family recognizes the risk. In general, clinical discussions of weight and behavior change should be patient-centered and participatory (vs. prescriptive). Nondirective questions (eg, "What concerns, if any, do you have about your child's weight?") may be less threatening to parents. Reflective listening and a respect for the family's values and current health practices are imperative. Both the parent and child should be engaged in the discussion of selecting target behaviors, and a specific plan with confidence ratings should be established (eg, "On a scale of 0-10, with 10 being the highest, how confident are you that you can eat 2 vegetables every day?"). For a sample 15-minute obesity prevention protocol based on these approaches, please refer to the recent American Academy of Pediatrics (AAP) recommendations for treatment.²

Mental health referral

Careful screening and assessment of comorbidities at the primary care level will be essential to provide comprehensive treatment to obese youth and their families. As with the need for specialist referrals for medical comorbidities, a referral to a mental health specialist may be necessary. The purpose of the referral is to provide the primary care practitioner with important information on diagnosis, risk, and treatment recommendations. A referral should be made anytime psychiatric or psychological concerns are impeding overall functioning (familial, academic, peer). Furthermore, an untreated psychiatric disorder or poor psychological functioning is likely to impede success in weight management.

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Unraveling the Mystery of Sudden Infant Death Syndrome (SIDS)

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The sudden infant death syndrome (SIDS) remains the number 1 cause of post-neonatal death in the US, despite the success of the “Back to Sleep” campaign launched in 1994 by the National Institutes of Child Health and Human Development and the “Back is Best” recommendations from the American Academy of Pediatrics in 1996. Although the specific cause for SIDS remains undiscovered, researchers are exploring the genetic basis for SIDS susceptibility, in attempts to establish more effective means to prevent sudden death in vulnerable infants. In the unfortunate and devastating event that an infant dies from SIDS, clinicians need to act quickly and sensitively to gather information that can ultimately provide answers to the grieving family. A systematic approach to this investigation can reveal a genetic condition that might have been responsible for the infant’s death, giving the family an invaluable opportunity for early detection and potential treatment if they choose to have another child. It is also important to offer families the tissue bank option as one way their tragedy can ultimately help save lives by furthering research into the genetic causes of SIDS.

SIDS risk factors

SIDS is currently defined as “the sudden and unexpected death of an infant less than 1 year of age, whose death remains unexplained despite a thorough autopsy, death scene investigation, and review of clinical history.”¹ Key recommendations targeting modifiable environmental risk factors for SIDS (see Table 1) led to a decrease in SIDS incidence from roughly 7,000 deaths each year in the US to just below 2,000 deaths a year. Approximately 95% of SIDS deaths occur before 6 months of age, with a peak incidence between 2 and 4 months of age.

Infants of all socioeconomic, racial, and ethnic groups are potentially vulnerable, though with varying risk. Infants at greatest SIDS risk include: preterm infants, especially those weighing less than 1,000 gm; infants who had intrauterine growth restriction; infants born to mothers with little or no prenatal care or under the age of 20 years; males; and African Americans and Native Americans. African American infants succumb to SIDS at a rate 2-3-fold higher than Caucasian infants.

Although 18% of SIDS victims are born prematurely, the vast majority of babies who die from SIDS are born at term and have no overt abnormalities that brought them to medical attention prior to the terminal event.

Researchers have proposed the triple-risk model in efforts to explain SIDS.² According to this model, the highest risk for SIDS occurs when 3 major risk factors overlap:

- Critical period of development (first 6 months of life)
- Pre- and post-natal environmental stressors (prone or side sleep position, nicotine exposure, soft bedding, overheating)
- Underlying vulnerability (possible brainstem abnormality, genetic susceptibility)

The underlying vulnerability risk factor has become a promising area of research. The ethnic disparity in SIDS, coupled with the occurrence of SIDS deaths despite improved compliance with modifiable risk factors, led investigators to consider a genetic basis for SIDS.

Educational Objectives

At the conclusion of this activity, participants will be able to:

- Describe the potential genetic diseases that can be uncovered in investigating a SIDS case, to offer families genetic counseling and opportunities to prevent sudden death
- Systematically investigate a SIDS case to rule out conditions that might explain the cause of death, to provide answers to families
- Discuss the tissue bank option with parents of a child lost to SIDS and explain how they can help speed scientific discovery to prevent SIDS

Genetic studies support the clinical impression that SIDS is heterogeneous, as opposed to a single entity and with a single genetic etiology.

Search for genetic causes of SIDS

Genetic studies in SIDS have been motivated by clinical, epidemiological, and/or neuropathological observations in SIDS victims, with subsequent pursuit of candidate genes in the following categories.

1. Genes for ion channel proteins, based on electrocardiographic evidence of prolonged QT intervals in SIDS victims
2. Gene for serotonin transporter and other genes in the serotonin network, based on decreased serotonergic receptor binding and other neuropathological findings in brainstems of SIDS victims
3. Genes pertinent to the early embryology of the autonomic nervous system (ANS) and with a link to the serotonin system, based on reports of ANS dysregulation in SIDS victims
4. Genes for nicotine metabolizing enzymes, based on evidence of cigarette smoking as a modifiable risk factor for SIDS and the most important risk factor after prone sleep position
5. Genes regulating inflammation, energy production, hypoglycemia, and thermal regulation, based on reports of postnatal infection, low birth weight, and/or overheating in SIDS victims

Research into the genetic causes of SIDS suggests that a number of genetically controlled networks may be involved in at least some cases.

A brief synopsis of findings to date is presented here. A comprehensive discussion can be found in recent review articles.^{3,4}

Investigation of SIDS in connection with the long QT syndrome (LQTS) susceptibility genes revealed that an estimated 5%-15% of SIDS cases are caused by a primary cardiac channelopathy. Among the remaining cases, genetic studies of the serotonergic system have documented specific polymorphisms in the serotonin transporter gene in SIDS and may provide initial clues to the ethnic disparity in SIDS. Furthermore, studies suggest that SIDS may be the result of protein-changing mutations in genes involved in the early embryology of the ANS, especially the *RET* gene and *PHOX2B*. (Editor's note: See accompanying article highlighting Dr. Weese-Mayer's research on the genetic basis of SIDS, pages 21-22 in this issue.)

At this stage, no defined genetic connection has been established between SIDS and nicotine metabolizing genes. It also is too early to assess the significance of some inconsistently observed associations between SIDS and the genes regulating inflammation, energy production and hypoglycemia. Overall, given the diversity of results to date, genetic studies support the clinical impression that SIDS is heterogeneous, as opposed to a single entity and with a single genetic etiology.

Table 1

IDENTIFIED FACTORS ASSOCIATED WITH HEIGHTENED SIDS RISK

- Prone or side sleep position for ANY sleep time
- Prenatal and postnatal cigarette exposure
- Soft bedding materials and soft sleep surface
- Sleeping on unsafe sleep surface, including an adult bed, couch, or armchair
- Overheating

Potential disorders that might appear as SIDS

When an infant dies suddenly and unexpectedly, it is essential that blood or tissue is collected to help the families and their physicians conclusively rule out known genetic disorders that might explain up to 20% of the deaths. In so doing, the family will have closure for the recent death and information for planning future pregnancies. The family can also be offered participation in research of additional SIDS candidate genes through tissue donation.

Congenital central hypoventilation syndrome (CCHS). CCHS is a related disorder of dysfunction in the ANS (the system that functions automatically to control breathing, heart rate, temperature regulation, and more).^{4,7} Children with CCHS typically present in the newborn period with immediate cyanosis upon falling asleep and a broad spectrum of physiologic abnormalities reflecting ANS dysregulation. However, recent data indicate that a subset of cases of CCHS can present after the newborn period even into infancy, later childhood, and adulthood. CCHS is inherited in an autosomal dominant manner, so knowledge of an affected infant is key to family planning and consideration of prenatal testing and/or pre-implantation genetics. Since a subset of children with CCHS are born to mosaic parents, both parents of an affected child should be screened for the child's *PHOX2B* mutation. With early diagnosis, proper management and ventilatory support, children with CCHS can grow into adulthood.

PHOX2B has been identified as the disease-defining gene for CCHS.^{6,7} DNA testing for mutations in the *PHOX2B* gene in "SIDS" cases should be performed with the *PHOX2B* Sequencing Test. One of the few laboratories in the world offering this test is housed at Children's Memorial Hospital.

Cardiac channelopathies. Cardiac channelopathy mutations can result in sudden death in infancy, childhood and adulthood. As mentioned

earlier, they account for up to 15% of cases thought to be SIDS. These mutations can be ascertained by analysis of DNA using the *FAMILION* tests with specific identification of long QT syndrome (LQTS), Brugada syndrome (BrS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). Because the clinical manifestations of cardiac channelopathy mutations respond to pharmacologic intervention, early diagnosis is essential to determine subject's risk and implement treatment strategies. This information is critical for families hoping to have more children and for identifying other affected family members.

Inborn errors of metabolism. MCAD (medium chain acyl CoA dehydrogenase) deficiency is another genetic disorder that can result in sudden death. It accounts for up to 5% of cases thought to be SIDS. MCAD is a disorder in which the body is unable to breakdown fats to make energy because the MCAD enzyme is missing or malfunctioning. Clinical presentation is typically in the first 6 years of life, primarily in the first 2 years, and rarely in adulthood. The symptoms may manifest after an intercurrent illness with decreased oral intake, leading to sudden death. Now that newborn state screening includes testing for inborn errors of metabolism, including MCAD, undiagnosed cases should be rare.

MCAD is an autosomal recessive disease for which prenatal testing is available. Treatment of MCAD deficiency includes avoidance of fasting for more than 10-12 hours, and consumption of carbohydrate-laden meals. Treatment with L-carnitine prevents low blood sugar during an intercurrent illness accompanied by a decreased appetite.

Systematic investigation of SIDS

There is no preparation for the unanticipated tragedy of an infant death. However, the steps that follow will require order and care so parents have as much available information as possible to ascertain the actual cause of the death and/or to contribute to future understanding of the cause of SIDS.

When an infant dies suddenly and unexpectedly, it is essential that blood or tissue is collected to help conclusively rule out known genetic disorders that might explain up to 20% of the deaths.

Center for Autonomic Medicine in Pediatrics

The first of its kind in the world, the Center for Autonomic Medicine in Pediatrics (CAMP) led by Debra E. Weese-Mayer, MD, at Children's Memorial Hospital is an interdisciplinary program that treats and studies autonomic nervous system (ANS) abnormalities in children, including disorders such as congenital central hypoventilation syndrome (CCHS).



In the photo: CAMP Medical Director Debra E. Weese-Mayer, MD, with Olivia Whalen, an 8-year-old patient with CCHS during an inpatient evaluation.

Inpatient evaluation. Central to CAMP is an inpatient evaluation that typically includes detailed physiologic recording during spontaneous breathing and assisted ventilation while the child is awake and asleep, in addition to assessment during various activities – exercise, playing video games, doing school work, reading, with and without respirator support. Many complementary tests from other pediatric disciplines are performed as well. These studies help establish the diagnosis, clarify the nature of the physiologic compromise in multiple organ systems affected by the ANS, provide comprehensive recommendations for ongoing ventilator or diaphragm pacemaker management, and design interventions to improve the quality of life for these otherwise quite capable children.

PHOX2B testing program. Years ago, Weese-Mayer and a colleague demonstrated that *PHOX2B* is the disease-defining gene for CCHS and have developed a blood test to confirm the diagnosis. More recently, Weese-Mayer and Lawrence Jennings, MD, PhD, director of Molecular Pathology, HLA and Immunogenetics, have developed another follow-up test that provides added detail on the *PHOX2B* mutations and hence on the severity of the clinical condition. As a result, the CCHS Without Walls genetic testing program is now offered at Children's Memorial, providing expanded services for individuals requiring the *PHOX2B* testing world-wide.

For more information about *PHOX2B* sequencing, please contact Lawrence Jennings, MD, PhD, at 773.880.8290 or 773.880.3015. More information on CAMP is available at <http://www.childrensmemorial.org/depts/autonomic-medicine>.

Death scene investigation. A death scene investigation should be completed to rule out accidental causes and to ascertain the temperature of the room and the sleep position when the infant was placed in the crib and when (s)he was found.

Clinical history. Review of the medical records and clinical history is essential to be certain there are no other underlying abnormalities that might account for the death.

Autopsy. Parents should be asked to consent to a thorough autopsy by a pediatric pathologist, with the aim to ascertain a specific cause of death not immediately apparent from the physical examination. A negative autopsy is requisite to term the death as SIDS. Tissue from each organ system should be divided into specimens such that ½ is frozen and ½ is fixed. The frozen tissue will allow for biochemical and genetic studies (present and/or future); the fixed tissue will allow for traditional diagnostic studies.

Virtual autopsy. For families who oppose an autopsy for religious reasons, a virtual autopsy may be considered via magnetic resonance imaging (MRI) or computed tomography (CT) of the body to identify focal abnormalities that might account for the death.

Blood collection or skin biopsy. If possible, blood should be collected to conduct genetic tests that might explain the cause for death, including *PHOX2B* testing to rule out CCHS, *FAMILION* screen to rule out cardiac channelopathy mutations, and MCAD screen to rule out inborn errors of metabolism. If no blood is obtainable, parents should be advised to consent to a skin biopsy in order to have tissue for future DNA testing and not lose an opportunity to learn about a potential genetic disease.

Facial photographs. Because faces can be typical for certain diseases, such as CCHS,⁸ it is suggested that parents consent to having digital photographs taken of the child’s face. The photograph size should allow the face to fill the viewfinder. Front view and both side views should be taken, with a horizontal ruler included in each of the 3 color photographs.

Autonomic dysregulation questions. It also might be useful to ask parents about symptoms of ANS dysregulation in the deceased child while their recollection is recent. (See Table 2 for a brief questionnaire.) Going on the premise that unexplained deaths labeled as SIDS are due to other disorders of ANS,⁵ the above steps and the questionnaire responses might inform the practitioner of other diseases to consider and other information that may help advise parents for future pregnancies.

DNA testing for mutations in the *PHOX2B* gene in “SIDS” cases should be performed with the *PHOX2B* Sequencing Test. One of the few laboratories in the world offering this test is housed at Children’s Memorial Hospital.

Table 2 SIDS CLINICAL QUESTIONNAIRE

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| <ul style="list-style-type: none"> • Any stillborns in the family going back 3 generations? • Any sudden deaths at any age in the family going back 3 generations? • Any family members with autonomic disorders, including CCHS, familial dysautonomia, Rett syndrome, or Hirschsprung disease? • Recent illness in the baby who died suddenly? • Usual sleep position for the baby who died suddenly? • Position when the baby was placed to bed the night of the final sleep? • Position when the baby was found at the time of death? | <ul style="list-style-type: none"> • Any symptoms of autonomic dysregulation in the deceased baby? Examples of specific symptoms: <ul style="list-style-type: none"> – Pupils dilated? – Difficulty swallowing? – Body temperature consistently below 98.6 degrees F? How was temperature taken? – Increased pain threshold (eg, not crying with blood draw)? – Turning blue during sleep? – Turning blue during feeding? – Abdominal distention? – Decreased frequency of bowel movements so they occur every 2-3 days instead of daily? – Decreased frequency of urination (number of diapers in a day)? – Cold fingers and toes? |
|--|---|

With too many infants still dying from SIDS each year, it behooves clinicians, researchers, and parents to combine efforts to achieve a common goal of preventing SIDS.

Tissue bank donation. Lastly, and especially if parents consent to an autopsy, they should be advised about an option to donate tissue to the National Institute of Child Health and Human Development (NICHD) funded University of Maryland Brain and Tissue Bank. This tissue bank collects tissue from individuals who have succumbed to many diseases and is an important tissue source for SIDS investigators. By donating tissue, the family is helping scientific inquiry that ultimately will prevent SIDS deaths. Parents who have donated tissue from autopsy to the tissue bank have described a sense of gaining comfort by helping others in their own grief. Arrangements between the hospital and the University of Maryland tissue bank (btbumab@umaryland.edu, phone: 800.847.1539 or fax: 410.706.2128) will need to be made to assure the proper collection of tissue.

Conclusion

With too many infants still dying from SIDS each year, it behooves clinicians, researchers, and parents to combine efforts to achieve a common goal of preventing SIDS. Until the genetic basis for SIDS is determined, it remains the responsibility of medical personnel to teach and model optimal SIDS risk reduction strategies, and for parents and caregivers to practice these prevention measures, thereby minimizing the role of environmental cofactors in the demise of vulnerable infants at heightened risk for SIDS. And in the unfortunate and devastating event of the sudden death of a seemingly normal infant, it is imperative that paramedics, medical personnel, and parents maintain a sense of order with the ultimate goal to provide answers for the grieving family.

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Piecing Together the Genetics of SIDS

VITA LERMAN



Debra E. Weese-Mayer, MD

The widespread “Back to Sleep” and “Back is Best” campaigns to prevent sudden infant death syndrome (SIDS) by placing babies to sleep on their backs and heeding other modifiable risk factors for SIDS successfully reduced the number of unexplained infant deaths, but not completely. More than 2,000 infants still succumb to SIDS in the United States each year, more often in African American families, even when parents did everything right. Because so many parents followed recommendations, yet babies were still dying, researchers turned to genetics.

Now a decade later, a genetic picture of SIDS susceptibility is starting to emerge. One of the major researchers determined to find the missing pieces within this genetic puzzle is Debra E. Weese-Mayer, MD, who leads the Center for Autonomic Medicine in Pediatrics (CAMP) at Children’s Memorial Hospital.

“Once we define the genetic profile of SIDS susceptibility, a pharmacological intervention that targets the underlying mechanism could be a possibility,” says Weese-Mayer. “We would also be able to identify high-risk infants through newborn screening or prenatal testing, and offer genetic testing to families to estimate risk.”

SIDS, serotonin and the autonomic nervous system (ANS)

Studies suggest that there might be different mechanisms accounting for the end result of sudden unexplained deaths, with bases in varied but potentially integrated systems. Weese-Mayer’s search for SIDS-related candidate genes has focused on the serotonin network, the autonomic nervous system, and their interrelationships.

“These are very promising directions for research,” says Weese-Mayer. “Altered function and development of the serotonin system in SIDS cases have been established in neuropathological studies. Our team is trying to identify the specific genetic variants responsible for these changes,” she explains. “Also, from clinical data collected before death, we know that there is a relationship between SIDS and problems in the ANS. Further, we know that serotonin influences regulation of breathing, heart rate, body temperature and the sleep-wake cycle, and is integral to the ANS.

Dysregulation of autonomic processes in SIDS might be caused by genetic variants within the serotonin network.

So dysregulation of these autonomic processes in SIDS might be caused by genetic variants within the serotonin network. Or, SIDS susceptibility might be a result of genetic variants within both the ANS and the serotonin system or in the genes regulating the interconnected mechanisms between these systems.”

The role of serotonin transporter gene variations

To date, Weese-Mayer’s team has contributed important pieces to the SIDS puzzle, especially with respect to the role of the serotonin transporter gene (*5-HTT*), which is a single protein that globally regulates serotonin re-uptake. Her research has established strong associations between SIDS and certain variations in the *5-HTT* gene that might explain the neuroanatomic findings in SIDS.

Specifically, Weese-Mayer’s team has shown that the long allele of the *5-HTT* gene promoter region and the 12 repeat allele of the intron 2 variable number tandem repeat (VNTR) region of the *5-HTT* gene appear together more frequently in African American SIDS cases. Yet the long allele of the *5-HTT* gene promoter region, alone, is more prevalent among Caucasian infants who have died from SIDS.

“These polymorphisms in the serotonin transporter gene may play an important role in SIDS susceptibility and may begin to explain the ethnic differences in SIDS risk,” says Weese-Mayer. “These findings also imply that the resultant change in serotonin levels may contribute to SIDS risk. Or, these polymorphisms may relate to SIDS risk through a developmental effect on raphe neurons, which release serotonin in the brainstem in early embryology. In fact, new findings from our collaborators in Italy suggest that the serotonin transporter promoter long allele combined with morphological developmental defects of the raphe nuclei predispose infants to SIDS.”

PHOX2B gene in SIDS

Weese-Mayer’s research also found that several distinct variations in the *PHOX2B* gene are more common in SIDS cases, specifically the intron 2 polymorphism and other mutations in exon 3. Earlier she and colleagues established *PHOX2B* as the disease-defining gene for congenital central hypoventilation syndrome (CCHS), a key disorder of ANS dysregulation. Weese-Mayer’s team also identified an increased incidence of SIDS in CCHS families, which led to more intensive scrutiny of *PHOX2B*. Her team discovered that specific mutations in other genes important in early embryology of the ANS may contribute some SIDS risk as well. As she explains, “Our underlying premise is that SIDS and CCHS are related within the rubric of disorders of ANS dysregulation.”

Tissue bank donations critical

Although researchers are advancing in the search to understand how the puzzle pieces fit together, the definitive SIDS gene or a set pattern of closely related genetic variants responsible for SIDS remains elusive. Weese-Mayer and her team are determined to reveal the genetic profile of SIDS through their relentless inquiry. Critical to this search are the tissue samples from SIDS cases, which she receives from the National Institute of Child Health and Human Development funded University of Maryland Brain and Tissue Bank. “By contributing to a central repository for rare diseases, parents can be assured that they and their loved ones are helping to advance science and unlock the mystery that took away the precious life of their child. Donating to the bank is truly the gift of a lifetime,” says Weese-Mayer.

Weese-Mayer’s team identified an increased incidence of SIDS in CCHS families and found that several distinct variations in the *PHOX2B* gene, the disease-defining gene for CCHS, are more common in SIDS cases.



FIGURE 1

1. A previously healthy 8-year-old girl presents with a 3-month history of persistent, intensely pruritic papules distributed symmetrically on her hands, thighs, elbows, and buttocks (Figure 1). Thorough questioning may also reveal:

- A. Negative review of systems
- B. No relief from oral diphenhydramine
- C. Positive family history of celiac disease
- D. All of the above



FIGURE 2

2. This 5-year-old boy presents with similar findings for 6 months duration (Figure 2). Skin biopsy to aid in the diagnosis of this condition should be performed:

- A. For histopathology and direct immunofluorescence of the freshest lesion
- B. For histopathology and direct immunofluorescence of the most established lesion
- C. For histopathology and tissue culture
- D. For histopathology, tissue culture and viral cultures



FIGURE 3

3. The diagnosis of dermatitis herpetiformis has been made in this 9-year-old boy (Figure 3). The most appropriate therapy includes:

- A. Oral corticosteroids
- B. Oral antihistamines and topical corticosteroids
- C. Gluten-free diet and oral dapsone
- D. Oral valacyclovir

Educational Objectives

At the conclusion of this activity, participants will be able to:

- Recognize the disorder described in the vignette and shown in the photographs
- Describe clinical features and differential diagnosis
- Describe management approaches

Importantly for the pediatric clinician, cutaneous findings may occur in the absence of, or frequently precede, gastrointestinal symptoms of celiac disease.

Answers: 1D, 2A, 3C

Discussion:

Dermatitis herpetiformis (DH) is considered a dermatologic hallmark of celiac disease (immune-mediated gluten sensitivity) in both children and adults, as 100% of affected patients demonstrate subclinical or latent gastrointestinal disease.¹ It typically presents as a persistent, intensely pruritic, papulovesicular eruption, and has a pathognomic appearance on skin biopsy with direct immunofluorescence. It is the most common immunobullous skin condition seen in adolescents, though it is quite rare in prepubertal children.² When DH does occur in younger children, it is most common in those aged 2 to 7 years, though it has been reported in an infant as young as 8 months of age.¹ Importantly for the pediatric clinician, cutaneous findings may occur in the absence of, or frequently precede, gastrointestinal symptoms. And while DH itself is rare, celiac disease is not: estimated prevalence in the United States is approximately 1:80 to 1:300 children,³ and may be increasing due to more heightened awareness of this diagnosis. Both DH and celiac disease are strongly associated with HLA (human leukocyte antigen) serotypes DR3 and DQw2,⁴ and approximately 10% of patients with DH will have 1 or more first-degree relatives with gluten sensitivity.⁵ Thus increased suspicion for this condition is warranted in a child with a positive family history.

Clinically, DH typically presents as extremely itchy, 1-3 mm erythematous papules and edematous plaques with superimposed vesicles, with striking predilection for the elbows, knees and buttocks in a symmetric distribution. Lesions are characteristically grouped, hence the "herpetiform" description, as they can resemble outbreaks of herpes virus. The nape of the neck and scalp may also be involved, as can any area of the skin. Mucosal involvement is rare, but if present, is usually asymptomatic. Patients may describe a prodrome of stinging or burning in the affected skin prior to the eruption of visible lesions. Due to the intense pruritus, clinicians

most often see unroofed or crusted lesions, as the primary lesion has been excoriated. Antihistamines and other anti-pruritic measures usually offer little relief.

In children, several unusual clinical variants have been described, including a case mimicking chronic urticaria,⁶ chronic deep nonpruritic dermal papules or nodules,⁷ palmoplantar erythematous plaques,⁸ and isolated palmar purpura.⁹ In all such cases, skin biopsy was diagnostic.

Differential diagnosis of DH in children includes: papular dermatitis/eczema, urticaria/papular urticaria, scabies, arthropod bites, chronic bullous disease of childhood (linear IgA dermatosis), pityriasis lichenoides et varioliformis acuta, erythema multiforme, lupus erythematosus, bullous pemphigoid, factitial dermatitis and vasculitis. The absence of typical atopic background, as well as the presence of vesicles on exam, should help to distinguish this entity from papular atopic dermatitis.

Diagnosis of DH is based on clinical findings, and confirmed with histologic and laboratory evaluation. Ideally, skin biopsy of the newest affected area should be performed, and immunofluorescent analysis of perilesional skin should always be included. Histopathology reveals classic features of subepidermal blistering, with groups of neutrophils and eosinophils at the dermal-epidermal junction. Direct immunofluorescence demonstrates pathognomic granular deposits of IgA at the tips of dermal papillae.

Once the diagnosis of DH is confirmed, an evaluation for the presence of celiac disease should be performed. Gastrointestinal symptoms may be minimal or absent at the time of presentation. Suggested testing includes measurement of IgA antibody to human recombinant tissue transglutaminase (TTG), recently confirmed as the most reliable diagnostic test for gluten sensitivity.¹⁰ In addition, baseline IgA levels should be measured, as those patients deficient in IgA will not have abnormally elevated levels of TTG IgA as otherwise expected.

Treatment of DH usually involves the combination of sulfone medication and dietary modification. Dapsone (initial dosage of 2 mg/kg/day) can provide dramatic relief of pruritic symptoms, typically within 24 to 48 hours after beginning therapy.¹¹ Baseline complete blood count and glucose-6-phosphate dehydrogenase (G6PD) level should be checked prior to initiating this medication, weekly blood counts repeated for the first month, and monthly checks continued for the next 5 months. Patients should be also counseled on potential side effects including hemolytic anemia, methemoglobinemia, leukopenia, gastrointestinal symptoms, peripheral neuropathy, headache, exfoliative rash, liver toxicity and lymphadenitis. Fortunately, these side effects are rare. Once suppression of symptoms has been achieved, dosage can be tapered as tolerated. If dapsone cannot be used or is ineffective, sulfapyridine may be an acceptable alternative.

In addition to pharmaceutical therapy, a strict gluten-free diet should also be strongly encouraged. In fact, many patients can achieve total resolution of skin disease by diet alone,¹² though dapsone may be necessary to control symptoms until dietary changes take full effect. Maintaining a gluten-free diet also leads to regression of small intestinal lesions, if present. DH and celiac disease have been associated with an increased risk of developing small bowel lymphoma, and adherence to a gluten-free diet may be protective against the development of this malignancy in affected patients.¹³ Sustaining this diet can be difficult for anyone but the most highly motivated patient, however, and referral to a nutritionist or support group (such as the Gluten Intolerance Group, www.gluten.net, or the National Foundation for Celiac Awareness, www.celiaccentral.org) may be helpful.

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Children's Memorial appoints new surgeon-in-chief



Marleta Reynolds, MD

Marleta Reynolds, MD, has been appointed as surgeon-in-chief and head of the Surgery Department, following her service in this role on the interim basis since September 1, 2008. Children's Memorial has been fortunate to have her wide-ranging expertise since 1985. Reynolds also serves as the division head of Pediatric Surgery, director of the ECMO Program

(extracorporeal membrane oxygenation or heart/lung bypass support), and a co-director of the Institute for Fetal Health. She holds the Lydia J. Frederickson Professorship in Pediatric Surgery and is a professor of surgery at Northwestern University's Feinberg School of Medicine. Reynolds is board certified in general surgery, pediatric surgery, cardiothoracic surgery, and surgical critical care.

New study probes genomics of preterm birth

Xiaobin Wang, MD, MPH, ScD, recently received a \$3 million grant from the National Institutes of Health (NIH) to conduct the first genome-wide association study of preterm birth in the multi-ethnic U.S. population, which could become a landmark study in the preterm field.

Wang's study is anticipated to lead to identification of novel genetic loci related to preterm birth. These findings may help develop a promising strategy to identify women at high risk for preterm delivery, and should have important implications for prevention of preterm birth and treatment of premature infants.

Wang is the Mary Ann & J. Milburn Smith Research Professor and director of the Smith Child Health Research Program at Children's Memorial Research Center. She is a professor of pediatrics at the Feinberg School.

Neonatal enterocolitis research

Isabelle De Plaen, MD, a neonatologist and researcher at Children's Memorial, was awarded a 2008 American Gastroenterological Association Foundation for Digestive Health and Nutrition Bridging Grant. Her long-term goals are to elucidate the molecular mechanisms that lead to neonatal enterocolitis (NEC), a deadly disease affecting the bowel of the premature infant, and to develop new therapeutic approaches.

De Plaen's laboratory has developed and characterized a neonatal mouse model of NEC. Using this model, she is studying the cell-specific role of the transcription factor nuclear factor- κ B, a major regulator of inflammation, in bowel injury and NEC. She expects that the results will have an important impact on the understanding of NEC pathogenesis and promote specific cell-targeted therapies to change the outcome of this devastating disease. De Plaen is a member of the Center for Digestive Diseases and Immunobiology of Children's Memorial Research Center and an associate professor of pediatrics at the Feinberg School.

Can cardiac stem cells improve heart function in cardiomyopathy?



Sunjay Kaushal, MD

Children's Memorial's cardiovascular-thoracic surgeon and researcher Sunjay Kaushal, MD, is the recipient of a 2-year grant from the Children's Heart Foundation for his study "Cell-Based Therapy for Congenital Cardiomyopathy Using Endogenous Cardiac Stem Cells." He hopes to determine whether cardiac stem cells can improve cardiac function in a

drug-induced cardiomyopathy model in mice that replicates the cardiomyopathy seen in congenital heart patients.

Kaushal's study will be an important first step in generating pre-clinical data to determine whether cardiac stem cells can reduce pediatric heart failure and improve the life expectancy in these clinically difficult cardiac patients. He is an assistant professor of surgery at the Feinberg School.

Researcher honored by Illinois Maternal & Child Health Coalition

Jenifer Cartland, PhD, director of Child Health Data Lab (CHDL) at Children's Memorial, was recently recognized with the Loretta Lacey Maternal and Child Health Advocacy Award from the Illinois Maternal & Child Health Coalition. CHDL provides focused analyses that help policy makers and public health planners identify local health needs and evaluate existing programs intended to promote health and prevent injury to children and adolescents. Cartland also is the co-director of the Center for Community Partnerships and Health Promotion, launched last year at Children's Memorial Research Center to bring together scholars and institutional collaborators to develop and promote evidence-based practices that address health risks in communities.

Pioneer Award from Children's Brain Tumor Foundation



Stewart Goldman, MD

Stewart Goldman, MD, medical director of Neuro-oncology at Children's Memorial, recently received the prestigious Pioneer Award from the Children's Brain Tumor Foundation for outstanding contributions in pediatric neuro-oncology and brain tumor research. Each year the organization honors an individual who has advanced the vision and pushed the boundaries in the field of neuro-oncology.

Goldman also is director of the hospital's Falk Brain Tumor Center, director of the Center for Clinical Trials Research for the Children's Memorial Research Center and associate professor of pediatrics at Northwestern University's Feinberg School of Medicine. He also serves as principal investigator at Children's Memorial for the National Cancer Institute-sponsored Pediatric Brain Tumor Consortium where he is a member of the consortium's steering, scientific, new agents and angiogenesis committees. Goldman is also the site principal investigator for the Children's Oncology Group Phase I Consortium.

Groundbreaking food allergy study seeks more participants: 500 families still needed to help researchers unlock causes of food allergies and propel cures

A groundbreaking Children's Memorial Food Allergy Study is gathering momentum with the support of the National Institutes of Health. Launched in 2005 in response to the rapid rise in the incidence of childhood food allergies and the lack of effective prevention and treatment, it is unprecedented in size, scope, and complexity. The study is designed to find answers to some fundamental questions: What are the causes of food allergy? How can food allergy be predicted and prevented? Are there alternative or better treatments for food allergy?

To date, the research team has recruited over 500 food allergy affected families. The team is seeking to enroll an additional 500 families to reach its goal of 1,000. The large sample size is necessary in order to have sufficient statistical power to study over a million genetic markers and environmental exposures that potentially affect food allergy. Children suffering with food allergies need your help to make this a landmark study of food allergy.

Please visit <http://www.childrensmrc.org/allergy> for more information about this study. If you would like to promote the study in your office with posters and flyers, please call or email us (see contact).

Who is eligible: This is a family-based study. An eligible family includes both biological parents and at least 1 food allergy affected child (age 0-21 years). Both parents and affected children must be willing to participate.

What is involved: Participants undergo routine clinical measurements (height, weight, blood pressure), a lung function test, allergy skin test, blood draw (10 ml or 2 tsp for allergy test and genotyping) and a questionnaire interview. Visits are conducted in Chicago and suburban locations by trained research staff. The study team will make every effort to accommodate the study family's schedule and preferred location.

Contact: Please call a toll free number 888.573.1833 or email allergystudy@childrensmemorial.org.

Research team: The food allergy study team consists of multidisciplinary investigators and is led by Xiaobin Wang, MD, MPH, ScD, director of Mary Ann & J. Milburn Smith Child Health Research Program, and Jacqueline A. Pongratic, MD, head of the Division of Allergy and Immunology at Children's Memorial Medical Center.

Sponsors: The study is supported by the National Institutes of Health (NIH), the Chicago Community Trust, Food Allergy Initiative and generous donors.

Bladder tissue engineering through nanotechnology

*Harrington DA, Sharma AK, Erickson BA, Cheng EY
World Journal of Urology 2008 Aug;26(4):315-322.*

The field of tissue engineering has developed in phases: initially researchers searched for “inert” biomaterials to act solely as replacement structures in the body. Then, they explored biodegradable scaffolds – both naturally derived and synthetic – for the temporary support of growing tissues. Now, a third phase of tissue engineering has developed, through the subcategory of “regenerative medicine.” This renewed focus toward control over tissue morphology and cell phenotype requires proportional advances in scaffold design. Discoveries in nanotechnology have driven both our understanding of cell-substrate interactions, and our ability to influence them. By operating at the size regime of proteins themselves, nanotechnology gives us the opportunity to directly speak the language of cells, through reliable, repeatable creation of nanoscale features. Understanding the synthesis of nanoscale materials, via “top-down” and “bottom-up” strategies, allows researchers to assess the capabilities and limits inherent in both techniques. Urology research as a whole, and bladder regeneration in particular, are well-positioned to benefit from such advances, since our present technology has yet to reach the end goal of functional bladder restoration. In this article, we discuss the current applications of nanoscale materials to bladder tissue engineering, and encourage researchers to explore these interdisciplinary technologies now, or risk playing catch-up in the future.

Vitamin D deficiency in children with chronic kidney disease: Uncovering an epidemic

*Ali FN, Arguelles LM, Langman CB, Price HE
Pediatrics 2009 March;123(3):791-796.*

BACKGROUND: Vitamin D deficiency in children adversely affects bone development by reducing mineralization. Children with chronic kidney disease are at risk for altered bone development from renal osteodystrophy and concomitant vitamin D deficiency. The pediatric Kidney Disease Outcomes Quality Initiative guidelines suggest measuring serum 25-hydroxyvitamin D (25[OH]D) levels if serum parathyroid hormone levels are above the target range for chronic kidney disease stages 2 and beyond, but the magnitude of vitamin D deficiency in children with chronic kidney disease is not well studied. **OBJECTIVES:** The purpose of this work was to determine whether children with chronic kidney disease had vitamin D deficiency, to evaluate whether the prevalence of vitamin D deficiency changed over time, and to examine seasonal and ethnic differences in

25(OH)D levels. **METHODS:** 25(OH)D levels in children with chronic kidney disease (stages 1–5) were measured over a 10-year period from 1987 to 1996. Data were also collected for a contemporary group of patients from 2005 to 2006. **RESULTS:** The prevalence of vitamin D deficiency ranged from 20% to 75% in the decade studied. There was a significant trend for decreasing 25(OH)D levels over the decade, both at the group and individual levels. Seasonal variation was noted. In our contemporary population with chronic kidney disease, the mean 25(OH)D level was 21.8 ng/mL; we found a prevalence of vitamin D deficiency of 39%. Black and Hispanic patients had lower levels of 25(OH)D than white patients. **CONCLUSIONS:** Children with chronic kidney disease have great risk for vitamin D deficiency, and its prevalence was increasing yearly in the studied decade. Contemporary data show that vitamin D deficiency remains a problem in these children. Sunlight exposure and ethnicity play a role in levels of 25(OH)D. Our data support the recent pediatric Kidney Disease Outcomes Quality Initiative guidelines for measurement of 25(OH)D levels in children with chronic kidney disease and secondary hyperparathyroidism.

Familial aggregation of food allergy and sensitization to food allergens: A family-based study

*Tsai HJ, Kumar R, Pongracic J, Liu X, Story R, Yu Y, Caruso D, Costello J, Schroeder A, Fang Y, Demirtas H, Meyer KE, O’Gorman MR, Wang X.
Clinical & Experimental Allergy 2009 Jan;39(1):101-109.*

BACKGROUND: The increasing prevalence of food allergy (FA) is a growing clinical and public health problem. The contribution of genetic factors to FA remains largely unknown. **OBJECTIVE:** This study examined the pattern of familial aggregation and the degree to which genetic factors contribute to FA and sensitization to food allergens. **METHODS:** This study included 581 nuclear families (2,004 subjects) as part of an ongoing FA study in Chicago, IL, USA. FA was defined by a set of criteria including timing, clinical symptoms obtained via standardized questionnaire interview and corroborative specific IgE cut-offs for > or =95% positive predictive value (PPV) for food allergens measured by Phadia ImmunoCAP. Familial aggregation of FA as well as sensitization to food allergens was examined using generalized estimating equation (GEE) models, with adjustment for important covariates including age, gender, ethnicity and birth order. Heritability was estimated for food-specific IgE measurements. **RESULTS:** FA in the index child was a significant and independent predictor of FA in other siblings (OR=2.6, 95% CI: 1.2-5.6, P=0.01). There were significant and positive associations among family members

(father-offspring, mother-offspring, index-other siblings) for total IgE and specific IgE to all the nine major food allergens tested in this sample (sesame, peanut, wheat, milk, egg white, soy, walnut, shrimp and cod fish). The estimated heritability of food-specific IgE ranged from 0.15 to 0.35 and was statistically significant for all the nine tested food allergens. **CONCLUSION:** This family-based study demonstrates strong familial aggregation of FA and sensitization to food allergens, especially, among siblings. The heritability estimates indicate that food-specific IgE is likely influenced by both genetic and environmental factors. Together, this study provides strong evidence that both host genetic susceptibility and environmental factors determine the complex trait of IgE-mediated FA.

Cathepsin L inhibition suppresses drug resistance in vitro and in vivo: A putative mechanism

Zheng X, Chu F, Chou PM, Gallati C, Dier U, Mirkin BL, Mousa SA, Rebbaa A.
American Journal of Physiology - Cell Physiology 2009 Jan;296(1):C65-74.

Cathepsin L is a lysosomal enzyme thought to play a key role in malignant transformation. Recent work from our laboratory has demonstrated that this enzyme may also regulate cancer cell resistance to chemotherapy. The present study was undertaken to define the relevance of targeting cathepsin L in the suppression of drug resistance in vitro and in vivo and also to understand the mechanism(s) of its action. In vitro experiments indicated that cancer cell adaptation to increased amounts of doxorubicin over time was prevented in the presence of a cathepsin L inhibitor, suggesting that inhibition of this enzyme not only reverses but also prevents the development of drug resistance. The combination of the cathepsin L inhibitor with doxorubicin also strongly suppressed the proliferation of drug-resistant tumors in nude mice. An investigation of the underlying mechanism(s) led to the finding that the active form of this enzyme shuttles between the cytoplasm and nucleus. As a result, its inhibition stabilizes and enhances the availability of cytoplasmic and nuclear protein drug targets including estrogen receptor-alpha, Bcr-Abl, topoisomerase-IIalpha, histone deacetylase 1, and the androgen receptor. In support of this, the cellular response to doxorubicin, tamoxifen, imatinib, trichostatin A, and flutamide increased in the presence of the cathepsin L inhibitor. Together, these findings provided evidence for the potential role of cathepsin L as a target to suppress cancer resistance to chemotherapy and uncovered a novel mechanism by which protease inhibition-mediated drug target stabilization may enhance cellular visibility and, thus, susceptibility to anticancer agents.

Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis:

A new paradigm for use

Paller AS, Eichenfield LF, Kirsner RS, Shull T, Jaracz E, Simpson EL, US Tacrolimus Ointment Study Group
Pediatrics 2008 Dec;122(6):e1210-1218.

OBJECTIVE: Long-term, safe and effective therapeutic options for managing the chronic relapsing nature of atopic dermatitis are essential for improving patient quality of life. To minimize the risks of continued topical corticosteroid usage and potentially reduce the incidence of flares, we tested the efficacy and safety of a rotational paradigm of initial brief application of topical corticosteroid followed by long-term intermittent application of non-steroidal tacrolimus ointment to previously inflamed sites of dermatitis. **METHODS:** In this 2-phase study, patients who were 2 to 15 years of age and had moderate to severe atopic dermatitis were randomly assigned to 4 days of twice-daily double-blind therapy with either alclometasone ointment 0.05% or tacrolimus ointment 0.03% (Phase I acute), followed by up to 16 weeks of twice-daily open-label tacrolimus ointment 0.03% (Phase I short-term). Patients whose disease stabilized underwent new randomization to double-blind tacrolimus ointment 0.03% or vehicle applied once daily, 3 times per week to clinically normal-appearing skin for up to 40 weeks (Phase II). Corticosteroid use was prohibited. **RESULTS:** Of 206 randomly assigned patients, 152 completed Phase I; 105 of 152 were randomly assigned into Phase II (68 tacrolimus ointment and 37 vehicle). There were no differences in adverse events between alclometasone and tacrolimus (Phase I) or between tacrolimus and vehicle (Phase II). In the acute period, alclometasone-treated patients showed greater improvement in atopic dermatitis signs and symptoms; thereafter, when all patients applied tacrolimus ointment (short-term), there were no differences. In Phase II, tacrolimus-treated patients had significantly more disease-free days compared with vehicle, significantly longer time to first relapse, and significantly fewer disease relapse days. **CONCLUSIONS:** For patients with stabilized moderate to severe atopic dermatitis, long-term intermittent application of tacrolimus ointment to normal-appearing but previously affected skin was significantly more effective than vehicle at maintaining disease stabilization, with a safety profile similar to vehicle.

Massage therapy in outpatient pediatric chronic pain patients: Do they facilitate significant reductions in levels of distress, pain, tension, discomfort, and mood alterations?

Suresh S, Wang S, Porfyrus S, Kamasinski-Sol R, Steinhorn DM
Paediatric Anaesthesia 2008 Sep;18(9):884-887.

BACKGROUND AND OBJECTIVES: This study was designed to look at the efficacy of adjuvant massage therapy in children and adolescents who presented to a chronic pediatric pain clinic for management. **METHODS:** After Institutional Review Board approval and informed consent and assent was obtained, all pediatric patients who presented to the outpatient chronic pain clinic at Children's Memorial Hospital from July 2006 to May 2007 were invited to participate in a study that offered massage therapy as an adjunct to conventional pain treatment. Patients (n = 80 sessions, 57 patients) were asked to rate their levels of distress, pain, tension, discomfort, and degree of upset mood on a scale of 1-5 (e.g. for distress 1 = very calm; 5 = very distressed) before and after massage therapy. Paired t-tests were used to compare pre- and postmassage ratings and probability values were corrected for multiple comparisons using the Bonferroni procedure. **RESULTS:** After massage therapy, patients reported highly significant improvement in their levels of distress, pain, tension, discomfort, and mood compared with their premassage ratings (all t-values >6.1, ****P < 1 x 10(-8)). To control for the possible effects of patients reporting improvements simply as a result of rating their symptoms, we collected control ratings before and after a comparable 'no intervention' time period in a subset of 25 patients. The 'no intervention' time period typically took place in the treatment room with the therapist present. Approximately 60% of the control ratings were obtained before the intervention and 40% were obtained after the massage therapy. None of the differences between the pre- and postratings associated with the 'no intervention' control time period were significant. In these same patients, the difference between the pre- and postmassage ratings were significant, all t-values >3.8, **P < 0.001.

Methods of investigation and management of infections causing febrile seizures

Millichap JJ, Gordon Millichap J
Pediatric Neurology 2008 Dec;39(6):381-386.

The management of febrile seizures is reviewed, with emphasis on methods of investigation and treatment of associated infections. Records of 100 consecutive febrile seizure patient-visits were examined retrospectively at an East Carolina University-affiliated hospital. Causes of fever and infection, viral and bacterial studies, antipyretic, antibiotic, and antiviral treatments, and indications for lumbar puncture were analyzed. Febrile seizures were first episodes in 64, simple in 76, and complex in 23 (prolonged, at 30-60 minutes, in 4). The mean age was 20 months. Viral studies in 26 patients were positive in 9 (35%). Bacterial cultures in 100 were positive in 5%, none from CSF. Antibiotics were prescribed in 65%, and antipyretics in 89%. Lumbar puncture was performed in 14 patients; 11 had complex seizures, and 3 simple. Of simple seizure patients, none was aged <12 months, and only 1 was aged <18 months at time of lumbar puncture. Clinical manifestations and complex seizures are the principal indications for lumbar puncture, and not patient age. Viral infection is the most common cause of fever, and bacterial infection is infrequent. Early viral diagnosis should lessen the emphasis on bacterial cultures, and lead to reduced use of empiric antibiotics.

Nitric oxide and beyond: New insights and therapies for pulmonary hypertension

Steinhorn RH
Journal of Perinatology 2008 Dec;28 Suppl 3:S67-71.

Persistent pulmonary hypertension of the newborn (PPHN) contributes significantly to the morbidity and mortality associated with meconium aspiration syndrome. This review article discusses new insights into the vascular abnormalities that are associated with PPHN, including the recent recognition of the importance of oxidant stress in its pathogenesis. Recent data are presented showing that treatment with high oxygen concentrations may increase production of oxygen free radicals. The rationale for the use of inhaled nitric oxide, and strategies for enhancing nitric oxide signaling are discussed. Finally, the rationale for new treatment approaches is reviewed, including inhibition of cyclic guanosine monophosphate-specific phosphodiesterases and scavengers of reactive oxygen species.



ACL

1. Which statement below is true?

- At the age of 14 years, female athletes have 5 times higher rates of ACL injuries than male athletes
- Girls and boys are equally at risk for ACL injuries
- ACL injuries are rare in 12-year-old girls
- ACL injuries are common in very young children

2. Non-operative treatment with physical therapy, bracing and activity modification is often recommended for ACL tears:

- Only in skeletally mature athletes
- In athletes of all ages
- In boys more often than girls
- In skeletally immature athletes until they reach skeletal maturity

3. Long-term follow-up of athletes who had ACL injuries shows:

- Increased risk of osteoarthritis
- No risk of degenerative joint disease after surgical reconstruction
- Higher risk for future problems in males
- None of the above

VITAMIN D

1. In its latest guidelines, the AAP considers infants, children, and adolescents to be vitamin D deficient when serum 25(OH)D levels are:

- < 11 ng/mL
- < 20 ng/mL
- < 40 ng/mL
- < 80 ng/mL

2. To receive the minimal daily intake of 400 IU of vitamin D, infants will require supplementation if:

- They are breastfed and drink less than 0.5 liter of formula fortified with vitamin D
- They are breastfed and drink less than 1 liter of formula fortified with vitamin D
- If they drink less than 2 liters of formula fortified with vitamin D
- If they drink less than 2.5 liters of formula fortified with vitamin D

3. Which medications increase the risk of vitamin D deficiency in children?

- Phenobarbital, carbamazepine, phenytoin
- Isoniazid, rifampin, theophylline
- Both a. and b.
- None of the above

OBESITY

1. What is one of the common psychiatric comorbidities in overweight or obese youth?

- Depression
- ADHD
- Bipolar disorder
- Schizophrenia

2. Which of the symptoms below may be a common risk factor for depression?

- Feeling a loss of control when eating and desire to compensate through exercise
- Decreased interest in previously enjoyable activities
- Use of purging to control weight
- Feeling stigmatized due to weight

3. Which of the symptoms below may be a common risk factor for disordered eating?

- Increased sleep
- Reduced levels of physical activity
- Anxiety in social settings
- Eating large quantities of food in secret and skipping meals at other times

SIDS

1. Collecting blood or tissue in a "SIDS" investigation helps to rule out which disorder as the actual cause of death?

- Coronary artery malformation
- Long QT syndrome
- Epilepsy
- Asthma

2. By DNA testing for mutations in *PHOX2B* gene, which disorder can be identified to explain a "SIDS" death?

- Congenital central hypoventilation syndrome (CCHS)
- Brugada syndrome
- MCAD deficiency
- Catecholaminergic polymorphic ventricular tachycardia (CPVT)

3. MCAD deficiency accounts for what percentage of cases thought to be SIDS?

- Up to 50%
- Up to 35%
- Up to 15%
- Up to 5%

DERMATOLOGY

1. Dermatitis herpetiformis (DH) may occur:

- Prior to the manifestation of asthma symptoms in children
- As a symptom of lupus
- Before the gastrointestinal symptoms of celiac disease
- In response to a viral infection

2. Typical clinical features of DH include:

- Symptomatic mucosal involvement
- Erythematous papules without pruritus
- Asymmetric distribution of lesions along the thighs
- Stinging or burning prior to eruption of visible lesions

3. DH has been associated with increased risk of developing:

- Small bowel lymphoma
- Malignant melanoma
- Esophageal cancer
- Liposarcomas

REGISTRATION FORM

Please Print:

_____	_____	_____
Last Name	First Name	Degree

Mailing Address		

_____	_____	_____
City	State	Zip Code

Phone Number		

Email Address		

_____	_____	
Date of Participation	Time to Complete Activity	

Evaluation

1. Were the activities' objectives met? Yes No

2. Do you feel the activity was fair,
balanced and free of commercial bias? Yes No

If no, please explain:

3. Will you change your practice as a result
of participating in this activity? Yes No

If yes, please explain:

If no, what factors are acting as barriers?

4. What topic areas would you like to see
covered in future educational activities?

*The Child's Doctor, Spring/Summer 2009*Please circle 1 correct answer for each question
in every article.**ACL**

1. a b c d

2. a b c d

3. a b c d

Vitamin D

1. a b c d

2. a b c d

3. a b c d

Obesity

1. a b c d

2. a b c d

3. a b c d

SIDS

1. a b c d

2. a b c d

3. a b c d

Dermatology

1. a b c d

2. a b c d

3. a b c d

Register and take CME quiz **online** at <http://www.childrensmemorial.org/cme>. • Or **mail** completed Registration Form to: Children's Memorial Hospital, *The Child's Doctor* CME Program, 2300 Children's Plaza, Box 40, Chicago, IL 60614-3394. • **Questions?** Please contact *The Child's Doctor* CME Program at: 773.880.6855 • **Deadline for registration:** For credit to be received, the Registration Form must be received (online or via mail) no later than June 15, 2010.

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Chicago

Suburban Outpatient Centers

Children's Memorial Outpatient Center in Arlington Heights
Northwest Community Hospital

Children's Memorial Outpatient Center in Glenview
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Children's Memorial at Central DuPage Hospital

Outreach Partner Locations

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Lake Forest Hospital/*Lake Forest*

Northwest Community Hospital/*Arlington Heights*

Prentice Women's Hospital at Northwestern Memorial Hospital/
Chicago

Sherman Hospital/*Elgin*

Silver Cross Hospital/*Joliet*

Swedish Covenant Hospital/*Chicago*

West Suburban Medical Center/*Oak Park*

Ranked #1 Inpatient Pediatric Volume

- Asthma
- Cardiology
- Cardiovascular surgery
- Dentistry
- Dermatology
- Endocrinology
- Gastroenterology
- Genetics
- Hematology/oncology
- Immunology/rheumatology
- Infectious disease
- Neonatology tertiary care (0-60 days)
- Nephrology
- Neurology
- Neurosurgery
- Ophthalmology
- Orthopaedics
- Otolaryngology
- Pediatric general medicine
- Pediatric general surgery
- Plastic surgery
- Pulmonary medicine
- Transplantation (liver, kidney, heart, intestine)
- Urology

Source: IHA Compdata, CY2007, based on volume in 7 county metropolitan area.



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