

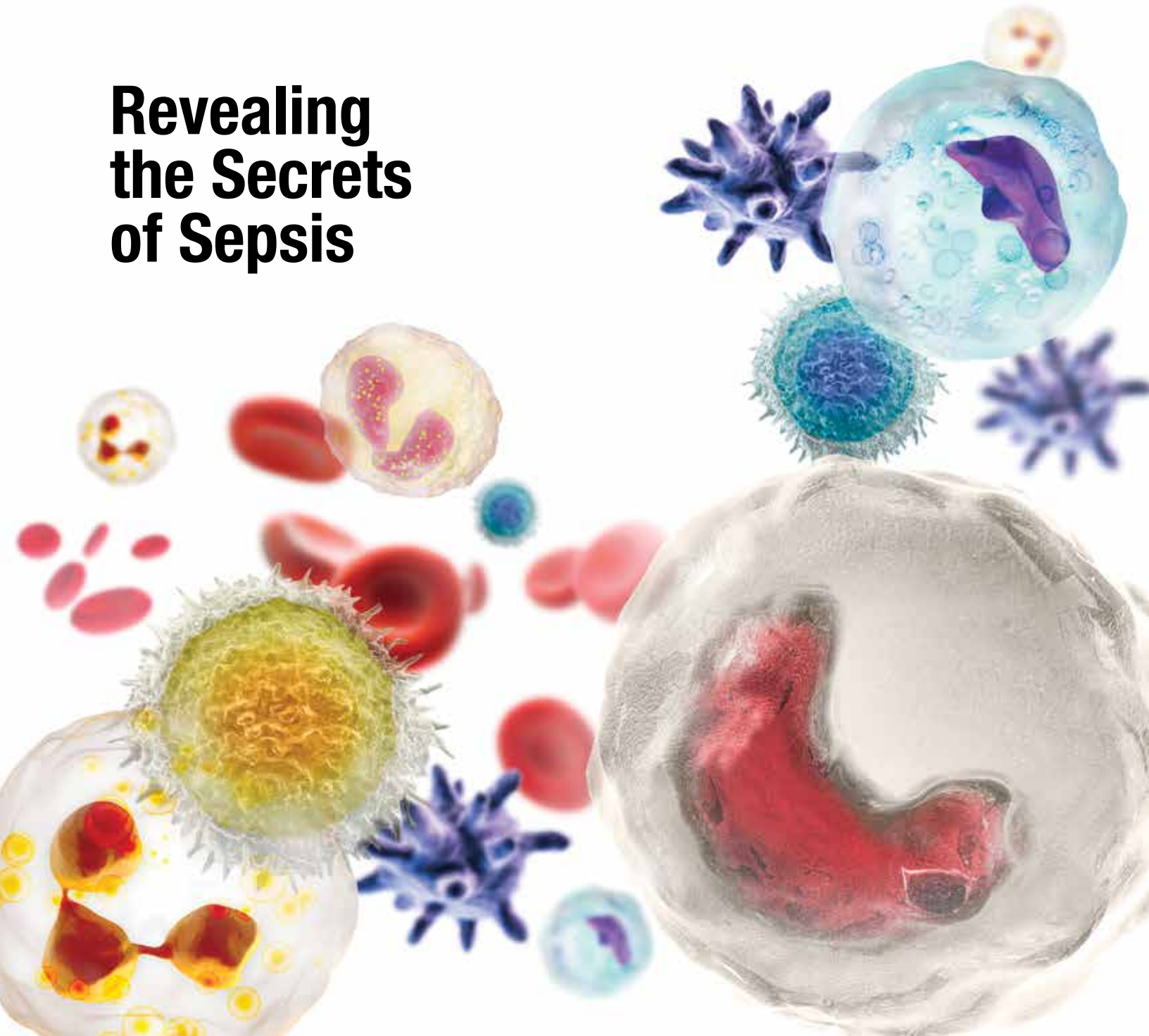
Fall/Winter 2015

Pediatrics

NATIONWIDE

Advancing the Conversation
on Child Health

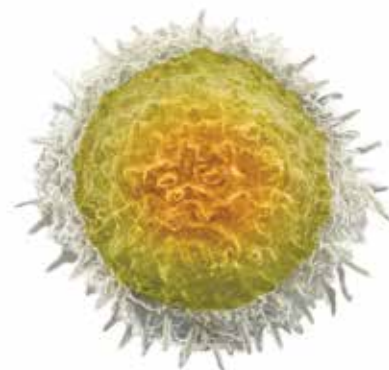
Revealing the Secrets of Sepsis



20 REVEALING THE SECRETS OF SEPSIS

Understanding how the immune system responds to sepsis has created a paradigm shift in patient care and provides targets for novel therapies.

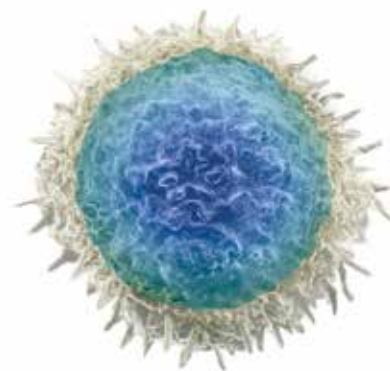
Monocytes and lymphocytes (B-cells and T-cells) are white blood cells that are being targeted by researchers to reverse sepsis-induced immunosuppression.



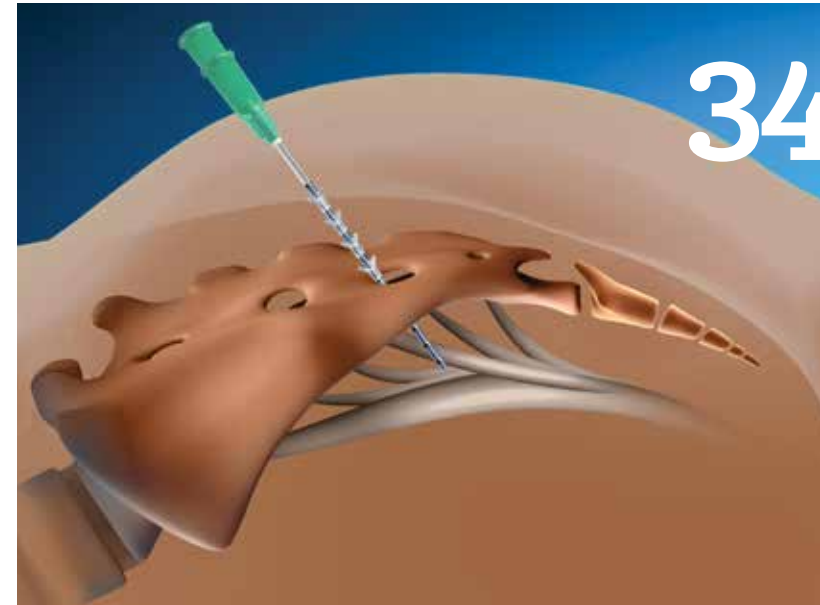
B-CELL LYMPHOCYTE



MONOCYTE



T-CELL LYMPHOCYTE



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“In an environment where costs are less likely to be reimbursed for preventable harm, harm prevention becomes not only the right thing to do for the patient but also the right thing to do economically.”

– Daniel Hyman, MD, Chief Quality and Patient Safety Officer, Children’s Hospital Colorado (page 17)

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“Blood is life-giving, but at a cost. We need to continue to work to capture more of the benefits and reduce the risks.”

– Mark E. Galantowicz, MD, Co-Director, The Heart Center, Nationwide Children’s Hospital (page 33)

Hidden Victims

Pediatricians acknowledge the emerging public health challenge of child commercial sexual exploitation.



Public health officials no longer think that human trafficking is just a problem in the developing world. Increasing awareness has focused attention on the exploitation of children in the United States, showing that medical professionals can uncover problems in their own backyards.

“I think it’s always been there,” says Jordan Greenbaum, MD, medical director of the Stephanie V. Blank Center for Safe and Healthy Children at Children’s Healthcare of Atlanta. “We just haven’t been looking for it and haven’t acknowledged it.”

Last year, Dr. Greenbaum’s hospital handled approximately 70 child sex exploitation cases. About eight years ago, the number was near zero, she says. She attributes the dramatic increase to growing awareness among law enforcement, social services and the medical community in the Atlanta area. “We’re getting to know more about what’s happening,” she says.

Dr. Greenbaum co-wrote a clinical report published in March in *Pediatrics* that outlines how health care providers can address this public health problem. “We realized that children who are victims are seeking medical attention, so the health care provider really does play a potential role in recognizing victims and offering services,” she says.

Dr. Greenbaum says medical professionals can do a better job identifying victims who may seek care for a

variety of reasons, such as sexual assault, physical injury, infection and contraceptive care. These victims may seek care in hospital emergency departments, family planning clinics, public clinics, urgent care centers and private offices.

The *Pediatrics* report identifies several risk factors for victimization: history of physical and/or emotional abuse and neglect, substance abuse problems, learning disabilities and gang involvement. Runaways, homeless children and gay, lesbian and transgender kids are also more likely to be victimized. “Most kids don’t see themselves as victims,” Dr. Greenbaum says. “Or even if they do, then they are afraid or ashamed to admit it, so they don’t come forward.”

What’s more, the patient may be hostile to health professionals and protective of his or her victimizer, who could be viewed as a friend or a lover. Providers will need to find a way to speak to patients alone, as the persons who brought them to the hospital or other medical setting may also be the ones exploiting them.

Mary Jo Bowman, MD, Pediatric Emergency Medicine Fellowship program director at Nationwide Children’s Hospital, says medical institutions need to increase training and education to reach more victims. “That’s part of my effort: to get that message out there and train people and make people aware so that we can identify more victims,” Dr. Bowman says.

Dr. Bowman, who’s also involved with the grass-roots anti-human trafficking organization Central Ohio Rescue and Restore Coalition, brought human trafficking expert Jeff Barrows, DO, to Nationwide Children’s to speak with emergency medicine and child abuse fellows a few years ago. In May, Dr. Barrows returned to the hospital to train nurses on how they can better identify sexual exploitation victims. “They’re not going to say, ‘I’m a victim of trafficking,’” Dr. Bowman says. “You have to look for the clues, and you have to be trained in the clues.”

— Dave Ghose

Methadone Weaning: The Role of the Pharmacist

Pharmacist-led methadone tapers are improving outcomes and reducing practice variation in pediatric intensive care units.

In neonatal and pediatric intensive care units, opioid use is necessary for controlling pain and as an adjunct to sedation during mechanical ventilation. However, after as few as five days of use, approximately 50 percent of patients will experience withdrawal once the medication is stopped. After 10 days of opioid use, 100 percent of patients will experience withdrawal.

Several characteristics make methadone ideal for weaning pediatric patients off opioids, including its 80-85 percent oral absorption and long history of use. Patients can even finish their methadone tapers at home, decreasing overall length of hospital stays in some cases.

“It’s an important distinction to make that these babies and children have developed tolerance and are experiencing withdrawal, not addiction,” says Joseph Tobias, MD, chief of the Department of Anesthesiology & Pain Medicine at Nationwide Children’s Hospital. “Research has shown that these patients are not more likely to abuse drugs and become addicts in the future.”

While methadone has been used to reduce withdrawal symptoms in pediatric patients since the 1990s, a recent study published in *Pediatric Critical Care Medicine* by a team of researchers at the University of Minnesota Masonic Children’s Hospital evaluates the role of the pharmacist in managing methadone tapers.

“We saw long-term gains in the pharmacist-managed tapers for methadone weaning, including decrease in withdrawal symptoms, shorter tapers and decrease in physician involvement,” says Sameer Gupta, MD, pediatric critical care physician at University of Minnesota Masonic Children’s Hospital and senior author of the study.

According to Dr. Gupta, the hospital instituted pharmacist-managed tapers more than five years ago, but after an increased emphasis on compliance in the last three to four years, the benefits became more profound.

“We found that methadone and lorazepam weans can be protocolized and handled more effectively by our Pharm.D colleagues, allowing physicians to spend more time on other aspects of patient care,” says Dr. Gupta, who is also assistant professor in the Division of Pulmonary and Critical Care Medicine in the Department of Pediatrics at the University of Minnesota.

In an editorial for the same journal, Dr. Tobias agrees that significant improvements in patient care can occur with the use of protocols such as those used by Dr. Gupta’s team. At Nationwide Children’s, pharmacists have been managing methadone tapers for more than a decade. “We identify patients who qualify for tapers and create a taper plan. We also decide the conversion dose, how to come off the infusion and start the oral meds,” explains Cheryl Sargel, Pharm.D, clinical pharmacy specialist in the pediatric intensive care unit (PICU). “Though the goal is standardization as much as possible, it’s important to make sure we’re taking a personalized approach from the beginning dose calculation to the completion of the taper.”

“Physical dependency and withdrawal remain a common problem following prolonged admission to the PICU,” Dr. Tobias says. “These problems have been reported with every sedative and analgesic agent used in the ICU setting. Using pharmacist-led protocols leads to a decrease in practice variation, which has been shown to improve outcomes.”

— Abbie Roth



Marijuana Exposure in Young Children

Researchers call for states to enact controls protecting all minors.

When states legalize marijuana for medical or recreational use, the number of children younger than 6 exposed to the drug spikes that year and continues to rise annually, researchers at Nationwide Children's Hospital report.

And the number of children classified as victims of major exposures — those requiring intervention for coma, seizures and changing blood pressure — also rises, national poison control center data shows.

The trends were consistent among the 20 states that legalized marijuana by 2013, according to a recent study led by Gary Smith, MD, DrPH, director of the Center for Injury Research and Policy at Nationwide Children's.

"We urge states, any time they're going to take the step to legalize marijuana for medical or recreational use, to include regulations to prevent young children from being exposed as part of their plan," says Henry Spiller, MS, D.ABAT, director of the Central Ohio Poison Center at Nationwide Children's and co-author on the study.

Spiller and colleagues call for child-resistant packaging in homes where children reside and educating buyers to keep marijuana products out of children's reach.

"These kids aren't trying to get high," Spiller says. "They watch their parents and mimic them."

The products — cookies, brownies, gummies and fizzy drinks — are familiar and more enticing than ground-up pot leaves and often have a higher concentration of the active ingredient tetrahydrocannabinol (THC).

Because marijuana has been a federally classified Schedule 1 controlled substance, its safety and effects haven't been rigorously studied. Pediatricians are concerned exposure may inhibit normal cognitive development. The drug may exacerbate symptoms of depression and anxiety and increase the risk of psychosis in adolescents and adults.

Colorado, the first state to legalize marijuana for medical and recreational use, began requiring child-resistant packaging in February.



To protect minors of all ages, states should take more steps and be willing to enact new regulations as needs arise, says Brendan Saloner, PhD, assistant professor of Health Policy & Management at the Johns Hopkins School of Public Health and author of a recent policy strategy study.

"Marijuana is changing, as are ways of consuming it and concentrating the dose," Dr. Saloner says. "It's important not to have the mentality that we'll solve this once for kids and be done with it."

Dr. Saloner urges states to take the following steps:

- Ban colorful packaging and marketing using animals and characters that attract children and adolescents.
- Highly tax marijuana products to make them too expensive for most adolescents to buy on the resale market.
- License pot retailers like liquor stores, limit the number and ban them near schools and playgrounds.

"We're concerned the marijuana industry could become a sophisticated, well-financed and influential industry like tobacco and alcohol that resists every new attempt at regulation," Dr. Saloner says.

The public and legislators are more likely to support restraint as states open the door to marijuana rather than add controls later, he says. "We think there's a potential to go beyond the inadequate strategies we have in dealing with tobacco and alcohol."

— Kevin Mayhood

Acetabular "Fleck" Sign Predictive of Labral Avulsion

A "fleck" sign on the postreduction CT scan calls for high suspicion of labral pathology, even in cases of congruent closed reductions.

Traumatic posterior hip dislocations and subluxations are typically treated with a closed reduction in pediatric patients. For patients who have a congruent hip reduction, the course of treatment often ends here. However, a new study published in the *Journal of Pediatric Orthopaedics* indicates that this course of treatment is missing near-complete avulsion of the posterior labrum in cases where an acetabular "fleck" sign is visible in the postreduction computed tomography scan.

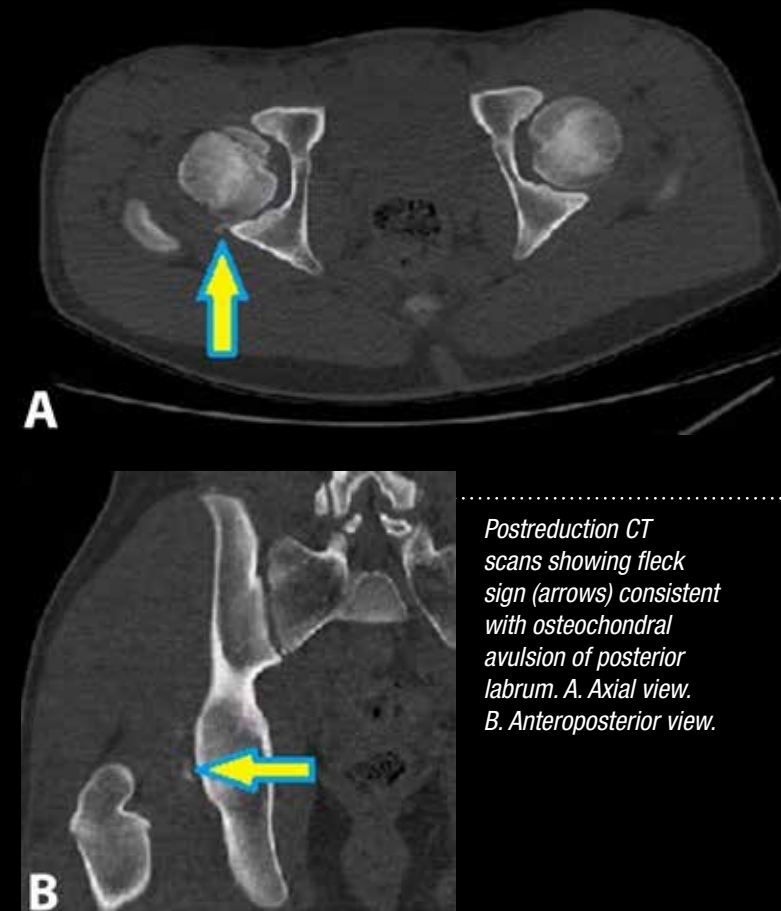
A team of researchers from Nationwide Children's Hospital is the first to describe the acetabular "fleck" sign, which was consistent with osteochondral avulsion of the posterior labrum in all cases in the study.

"During surgery, all of these patients were noted to have a labral injury pattern not previously recognized," says Kevin Klingele, MD, chief of the Department of Orthopaedics at Nationwide Children's and senior author on the paper.

Eight patients had postreduction CT scans revealing a posterior acetabular wall "fleck" sign, which is suggestive of osteochondral injury. The small bony fragment was consistently displaced at least 2-3 mm in all patients, with the majority of the posterior wall remaining intact.

Notably, the closed reduction for seven of eight of these patients was congruent. In the first case, the closed reduction was not congruent, so an open reduction was completed. During surgery, the labral avulsion was found. In the next case, the patient had a congruent closed reduction, but surgery was indicated for repair of a femoral head fracture. Again, labral avulsion was found during the operation.

"The majority of patients in the study had congruent hip reduction, but a significant injury was still found," Dr. Klingele says. "We recommend a high level of suspicion for this type of labral pathology and surgical repair when the acetabular fleck sign is identified with hip subluxation or dislocation."



Postreduction CT scans showing fleck sign (arrows) consistent with osteochondral avulsion of posterior labrum. A. Axial view. B. Anteroposterior view.

According to Dr. Klingele, studies in adults have shown that untreated labral insufficiencies are associated with joint problems down the road, and this may be true for pediatric patients as well.

The incidence of labral pathology in pediatric patients after traumatic hip dislocation is unknown, however. This study begins a new discussion on the management of these patients.

"Based on what I've seen and the reproducibility of the findings of this study, if I see the fleck sign, I will open," Dr. Klingele explains. "And so far, when I do, I've found labral pathology — even in cases of a congruent hip reduction."

— Abbie Roth



Severely Obese by Kindergarten: What's a Doctor to Do?

The numbers of children and adolescents with severe obesity have continued to rise in the past 30 years, but only a few centers provide evidence-based care for severe childhood obesity.

Childhood obesity affects 17 percent of children in the United States, and nearly one-third of these children are severely obese. The prevalence rates of children with severe obesity are increasing rapidly, setting kids up for a lifetime of health issues, from early atherosclerosis and hypertension to type 2 diabetes and psychological problems.

Studies indicate that children with severe obesity respond poorly to conventional lifestyle interventions. Although bariatric surgery can be an effective treatment, long-term outcomes are still being studied, and it is often inaccessible to most families due to the limited availability of adolescent programs offering the option.

However, according to a recent paper from the Institute of Medicine's (IOM) Roundtable on Obesity Solutions, these poor responses to lifestyle interventions may be because current approaches assume that all children and adolescents with obesity or severe obesity are a homogenous group. The process of clinical subtyping could identify variations in severe childhood obesity, leading to improved treatments.

Ihuoma Eneli, MD, medical director of the Center for Healthy Weight and Nutrition at Nationwide Children's Hospital and primary author of the IOM discussion paper, and colleagues agree that research characterizing this population of children with severe obesity is the first step to unraveling appropriate treatment options.

The American Academy of Pediatrics Institute for Healthy Childhood Weight and the Children's Hospital Association have already partnered to begin the process of clinical subtyping for severe obesity, creating the Expert Exchange, an interdisciplinary group of experts from tertiary care obesity programs at 21 children's hospitals nationwide. The Expert Exchange will focus on children ages 0 to 5 years old. The project will include qualitative feedback from clinicians, families and children, all of whom are integral to determining how individual characteristics may form recognizable subtypes.

"Currently, there is a deficit in our knowledge about early-onset childhood obesity, but children who present with severe obesity by age 5 are a subgroup that is distinct and rare enough to potentially offer a number of specific clinical subtypes," says Dr. Eneli, who is also a professor of Clinical Pediatrics at The Ohio State University College of Medicine. "By broadly examining etiological and clinical characteristics across several stages of the life cycle — early infancy, toddlerhood and preschool phase — research would cut across several developmental stages, environmental settings and caregivers, ultimately leading to a promising framework on which further, more effective treatment can be based."

"The Expert Exchange initiative offers a chance to advance the care of children and adolescents with severe obesity," explains Dr. Eneli. "And the perspective of clinicians who treat these young children is an invaluable part of the process of clinical subtyping."

— *Tiasha Letostak, PhD*

Suicides Rising Among Young Black Children, Rural Adolescents

Researchers are parsing data for trends and intervention targets.

Researchers in central Ohio are gaining surprising insights they hope will lead to fewer children and adolescents committing suicide.

While the suicide rate among white children 5 to 11 years old has declined since 1993, the rate among black children in the same age group has nearly doubled.

"The rates for suicide in this age group are low, but we're seeing an increase and we can't point to any factors as the causes. That's concerning," says Jeff Bridge, PhD, principal investigator in the Center for Innovation in Pediatric Practice in The Research Institute at Nationwide Children's Hospital, who led the national age-group study.

In a second study, researchers found suicide rates increase with age, and from 1996 to 2010, "nearly 67,000 youths age 10 to 24 died by suicide nationally," says Cynthia Fontanella, PhD, assistant professor of Psychiatry and Behavioral Health at The Ohio State University, who led the second study. "The figure is just shocking."

Researchers also found adolescents and young adults in the most rural parts of the United States take their own lives at nearly twice the rate as those from the most urban counties. And the disparity appears to be growing.

Drs. Bridge and Fontanella are investigating reasons for the trends. They speculate that young black children, particularly boys, may be exposed to more violence and traumatic stress; experience an early onset of puberty accompanied by greater incidence of depression and impulsive aggression; and may be less likely to seek counseling. Rural youths have far less access to mental

health care, are more likely to be socially isolated and have more open access to guns.

Until the Bridge-led study, reported suicide rates consistently have been higher among whites than blacks across the age spectrum. The researchers found the hidden trend inside data that showed overall suicide rates among children younger than 12 were steady. They were so surprised, Dr. Bridge says, that they waited an extra year for data to confirm their analysis. The rate of black suicides rose from 1.36 per million children in 1993-1997 to 2.54 per million in 2008-2012. The rate among white children fell from 1.14 to 0.77.

The Fontanella-led study found the suicide rates were 19.9 per 100,000 males and 4.4 per 100,000 females in the most rural U.S. counties, and 10.3 per 100,000 males and nearly 2.4 per 100,000 females in the most urban. Suicide rates among rural males and females climbed while the rate among urban males declined and the rate among urban females held steady. In both studies, males committed suicide four times more often than females.

The researchers are now working with the Ohio Department of Mental Health and Addiction Services and county alcohol, drug addiction and mental health boards to identify high-risk areas and factors that precipitate suicide attempts among children and youths.

"We believe if we can understand where and why the rates are high, we can target interventions better," Dr. Fontanella says. "We're hoping this will drive prevention in Ohio and nationally."

— *Kevin Mayhoo*



New Drug Advances Cystic Fibrosis Care

Orkambi helps reduce infections and slows loss of lung function in some patients.

Matt Hennessey knew he was on the experimental medicine and not a placebo just days after he began participating in a drug trial. He felt better.

The addition of Orkambi pills to his daily routine was just another part of his maintenance care for cystic fibrosis. Twice each day he donned and inflated the vest that shakes the mucus coating his lungs and stomach to prevent it from becoming stagnant. And he continued swallowing other medicines and inhaling aerosols for the same reason.

“Every other month for 13 years, I would get an infection and go on oral antibiotics and more intensive aerosols,” says Hennessey, 23, of Columbus, Ohio. “Since starting Orkambi, I’ve been on oral antibiotics one time in two years. It’s a remarkable shift, a tangible improvement in my life.”



Dr. McCoy and Hennessey participated in the groundbreaking Orkambi clinical trial.

The Food and Drug Administration approved Orkambi in July. Patients who received the drug during the trials improved slightly. Compared to patients who received placebos, the treatment group’s lung function was 4.3 to 6.7 percent better. They also had 30-39 percent fewer pulmonary exacerbations — infections — and significantly fewer exacerbations that required hospitalizations and intravenous antibiotics.

Maintenance is important with a debilitating disease, says Karen McCoy, MD, chief of the Section of Pulmonary Medicine at Nationwide Children’s Hospital. “This may help some people while we develop an even better drug.”

Dr. McCoy, who led the drug trial in central Ohio, is principal investigator for the Cystic Fibrosis Therapeutic Development Center and the director of the Cystic Fibrosis Center at the hospital.

According to the Cystic Fibrosis Foundation, more than 1,800 mutations affect the cystic fibrosis gene. Orkambi is the first drug approved for the form of cystic fibrosis affecting half of the 30,000 U.S. patients.

Orkambi is actually two drugs. Ivacaftor, sold as Kalydeco, dramatically improves the lives of people with a gene defect that affects less than 10 percent of the cystic fibrosis population, says Dr. McCoy. Ivacaftor alone can’t do much for the larger group of cystic fibrosis patients, but combined with lumacaftor, the drugs help epithelial cells function better.

“The combined drugs do improve the quality of life for some patients,” Dr. McCoy says. “With each infection, a patient may not return to the same lung function he or she had before. Treatment for acute exacerbations takes time and the drugs used are very harsh and can be damaging to other organs, and expensive. For all those reasons, going longer between treatments is a neat marker a patient is better than before the drug.”

For Hennessey, the decreased number of infections and improved quality of life has made Orkambi a valuable part of his maintenance program.

— Kevin Mayhood

Sickle Cell Disease: Global Disparities in Prevalance and Outcomes

An estimated 300,000 to 500,000 babies worldwide are born with sickle cell disease (SCD) each year. In Africa and India, where SCD is most prevalent, newborn testing is not performed, and many children with sickle cell disease die before they are even diagnosed. “Their death certificates will say malaria, anemia or pneumonia, though the real cause is sickle cell disease,” says Patrick McGann, MD, assistant professor in the Department of Pediatrics at University of Cincinnati.

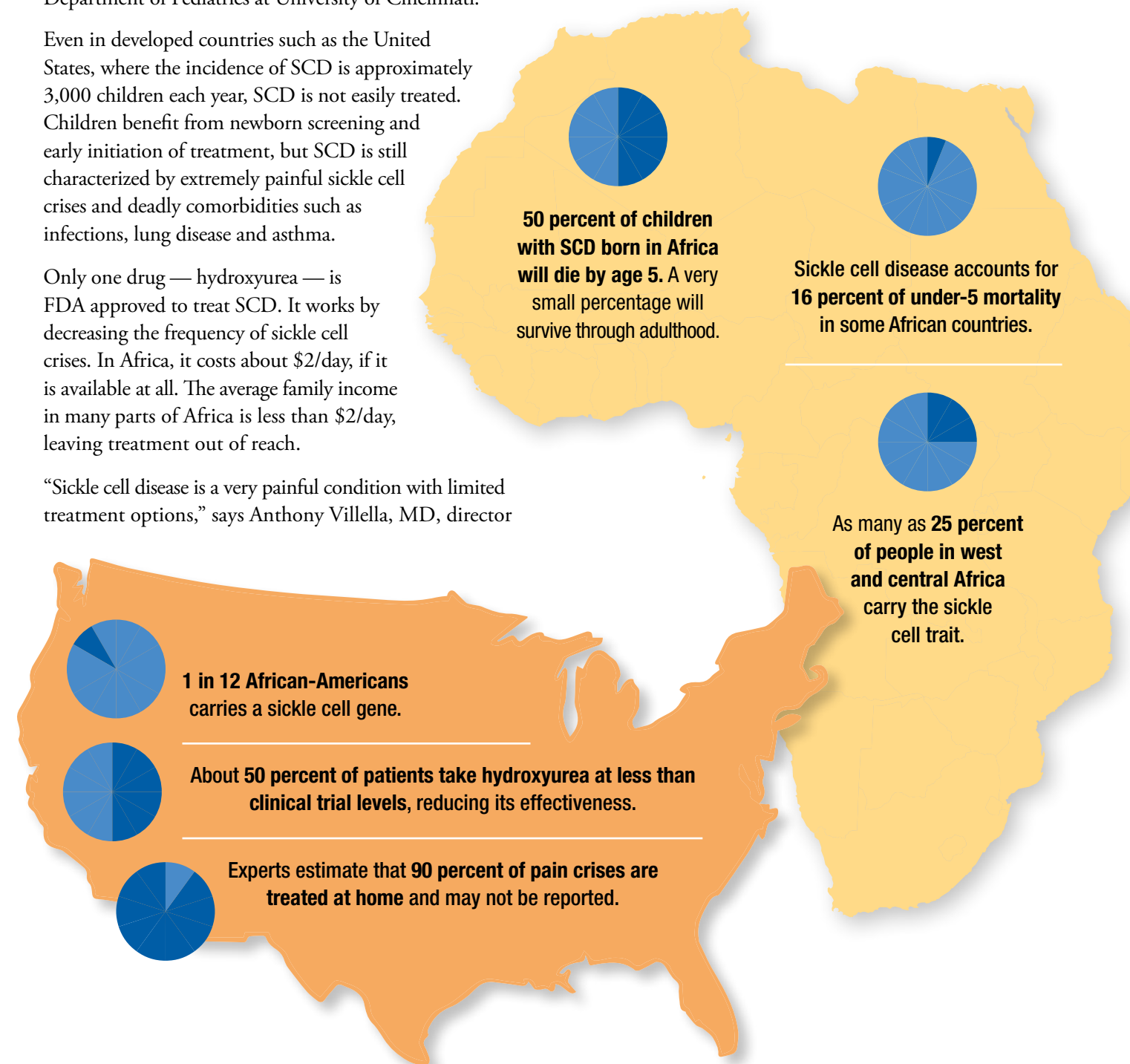
Even in developed countries such as the United States, where the incidence of SCD is approximately 3,000 children each year, SCD is not easily treated. Children benefit from newborn screening and early initiation of treatment, but SCD is still characterized by extremely painful sickle cell crises and deadly comorbidities such as infections, lung disease and asthma.

Only one drug — hydroxyurea — is FDA approved to treat SCD. It works by decreasing the frequency of sickle cell crises. In Africa, it costs about \$2/day, if it is available at all. The average family income in many parts of Africa is less than \$2/day, leaving treatment out of reach.

“Sickle cell disease is a very painful condition with limited treatment options,” says Anthony Villella, MD, director

of the Comprehensive Sickle Cell and Thalassemia Program at Nationwide Children’s Hospital. “Historically, there has been a serious lack of awareness and research funding for the development of novel therapies for sickle cell disease. Now, pharmaceutical companies are starting to commit resources to sickle cell research. I am optimistic that we will have more options in the future.”

— Abbie Roth



EXIT 1A

A PRACTICAL GUIDE TO BEGINNING CLINICAL RESEARCH

EXIT  ONLY

You wouldn't travel to unknown destinations without a map or GPS, so why do clinical research without a plan? Here's what you need to know to get started.

by *Tiasha Letostak, PhD*

Although the process for clinical research varies from institution to institution, the initial hurdles are often the same. From establishing clear protocols and outlining a detailed timeline to developing a reasonable budget and ensuring compliance with regulations, transitioning from the role of a physician with a research question to that of a principal investigator is a marathon, not a sprint.

This is why the support and resources that institutions offer — from their institutional review boards to database development — are vital to the success of clinical studies, especially for physicians who are just starting out.

A key first step in designing or reviewing clinical research projects is the feasibility process. Feasibility involves assessing the study to determine budgetary and scientific adequacy, subject availability, staff availability, specific training or equipment needed, and how the study differs from the standard of care.

“We have instituted a mandatory feasibility meeting to review every clinical research study at our institution,” says Grace Wentzel, CCRP, director of Clinical Research Services at Nationwide Children's Hospital. “Doing so ensures that details of the study, from the exact procedures that will occur and the costs involved to processes designed to eliminate the risk of a bill for a research procedure getting released to a subject's insurance, are clearly outlined prior to study initiation.”

With respect to funding, clinical research can be industry sponsored, federally funded (NIH, CDC, etc.), funded by foundation or small organization grants, or internally funded by a department or intramural program.

“Regardless of the funding source or where the science is initiated, conducting a feasibility assessment for all clinical research studies is beneficial to both the investigator and the institution,” says William E. Smoyer, MD, vice president of Clinical and Translational Research in The Research Institute at Nationwide Children's. “The feasibility assessment also serves as an initial evaluation of scientific importance — also known as the ‘so what?’ test — as well as assessing adequacy of study staff availability, and ensures there is an adequate study population and a sufficient budget.”

Once the study budget is established, IRB submission is approved, and contracts are reviewed, approved and signed by the institution, an initial launch or award meeting occurs and the sponsor hosts a site initiation visit, if applicable. This is the finish line of the feasibility process, and the beginning of study recruitment and enrollment.

The feasibility assessment involves determining scientific importance, staff availability, subject availability, and budgetary adequacy for a clinical research study. This checklist outlines the process prior to initiation of participant recruitment.

EXIT #1: SCIENTIFIC IMPORTANCE

Goals should be attainable with the proposed study design, the study should contribute to the literature, and there should be adequate scientific support from other investigators or potential collaborators.

- Will this study further our knowledge about this disease and advance science?
- Will it lead to academic gains or publication opportunities?
- Do other investigators think the study is scientifically reasonable? Are they supportive? Should they be invited to become collaborators on the study?
- Will the study design meet its objectives?

EXIT #2: STAFFING AVAILABILITY

Assessing the adequacy of staff and resources is necessary and beneficial for both the principal investigator and the institution.

- Does the principal investigator have enough time to commit to leading a trial?
- Do colleagues and/or collaborators have enough time for the trial?
- Who will manage the study?
- Will institutional resources be used for clinical research? (E.g., study nurse and coordinator, regulatory/IRB coordinator.)
- Will staff require training?

EXIT #3: SUBJECT AVAILABILITY

Subject availability is based on not only the particular study in question and its study design but whether there are competing studies recruiting the same patient population.


- Is this a “safety only” study or a treatment study?
- Are there any competing studies recruiting the same patient population?
- Does the study minimize the risk to patients?
- Will the participants have access to a novel treatment?
- Do the benefits outweigh the risks of participation?
- Will it be difficult to recruit subjects? Is a placebo involved?
- How much does the study differ from standard of care?

EXIT #4: BUDGET DEVELOPMENT

The overall goal of budget development is to ensure that all costs will be covered, from costs associated with recruitment to those incurred for study procedures and participant incentives.

- How many patients will be recruited?
- Which procedures will occur at each visit?
- Will the patient receive incentives?
- Is pharmacy involved?

NEXT EXIT: INITIATE PARTICIPANT RECRUITMENT

 Join the conversation. What tools do you use to do feasibility planning for your clinical research? Lend us your voice at PediatricsNationwide.org/Clinical-Research.



BETTER CARE



BETTER BUSINESS

The changing economics of health care are forcing hospitals to find solutions that are good for patients and for the bottom line.

..... by Dave Ghose

A puzzled neonatologist approached Richard McClead, MD, after he spoke at a conference in Boston. It was 2010, and Dr. McClead just finished detailing a new initiative at Nationwide Children’s Hospital to reduce the time babies spend in the hospital’s neonatal intensive care unit. “Why would you do that?” asked the neonatologist.

Nationwide Children’s was challenging the conventional financial wisdom of the time. At the neonatologist’s hospital, the NICU was a “cash cow.” The longer a preemie stayed in the unit, the more money the hospital made. “He was implying that, ‘If I cut length of stay in my NICU, my hospital administrators are going to be all over me because we’re losing money,’” recalls Dr. McClead, associate chief medical officer for Nationwide Children’s.

Today, the changing economics of health care are forcing providers everywhere to redesign how they treat patients. The goal is better care and better business. No longer can hospitals expect payment for services in all circumstances — especially if they’re to blame for a costly “serious safety event” such as a wrong-site surgery. “In an environment where costs are less likely to be reimbursed for preventable harm, harm prevention becomes not only the right thing to do for the patient but also the right thing to do economically,” says Daniel Hyman, MD, chief quality and patient safety officer for Children’s Hospital Colorado.

DO NO HARM

In the traditional fee-for-service economic model, hospitals aren’t always incentivized for harm reduction. They get paid even if they’re treating a hospital-acquired condition such as bedsores or catheter-associated urinary tract infections. “The health care industry is about the only industry where you’re paid to hurt people,” Dr. McClead says. “It sounds over the top, but it’s true. We get paid for things we do poorly.”

Nationwide Children’s began to upend this model in 1994 when the hospital created Partners for Kids (PFK), a physician-hospital organization comprising 760 physicians. Partners for Kids is the oldest and one of the largest exclusively pediatric accountable care organizations (ACOs) in the United States. As an ACO,

Partners for Kids takes on the full financial and clinical risk for Nationwide Children’s Medicaid enrollees, functioning much like an insurance company. Instead of receiving payment for services, the hospital takes home a fixed amount per enrollee per month. The approach gives the hospital a financial incentive to reduce costs. “And much of those costs arise from causing preventable harm to our patients,” Dr. McClead says.

A wide-ranging quality improvement program has coincided with the new economic approach. In 2008, the hospital set an ambitious goal to eliminate all preventable harm. Full-time quality improvement personnel increased from eight in 2007 to 33 in 2012, while the budget grew from \$690,000 to \$3.3 million. Multidisciplinary teams were deployed to focus on the most significant problem areas, such as bedsores, adverse drug events and hospital-acquired infections, including catheter-associated urinary tract infections, ventilator-associated pneumonia and surgical-site infections.

The initiative has produced impressive results. The rate of serious safety events — variations from expected practice that result in significant harm — dropped dramatically, from 6.7 per quarter to 1 (an 85.1 percent drop). Also decreasing were common preventable conditions such as bedsores, adverse drug events and hospital-acquired infections.

A 2013 study published in *The Journal of Pediatrics* reported the total annual estimated cost of preventable harm at Nationwide Children’s dropped from \$8.37

million in 2010 to \$6.53 million in 2012, a 22 percent decrease. “Each one of those harm events not only causes harm for the patient but also causes financial harm to the system,” Dr. McClead says.

Children’s Hospital Colorado also has experienced dramatic results since it launched its own major quality improvement program. Over the past two years, the hospital saw the number of serious safety events drop by about two-thirds, while the rate of hospital-acquired conditions has decreased by 30 percent, says Dr. Hyman, who joined Children’s Hospital Colorado in 2008 to fill the newly created position of chief quality officer.

In 2015, the Aurora, Colorado, hospital won the American Hospital Association-McKesson Quest for Quality Prize. Other honorees included Nationwide Children’s, Duke University Hospital in Durham, North Carolina, and Schneck Medical Center in Seymour, Indiana. Only three children’s hospitals have ever received this recognition.

“We’re doing this because it’s the right thing to do for patients,” Dr. Hyman says. “We’re doing this because the economics make sense. And we’re doing this because our organizational leadership believes it’s the right thing for us to do to be the best hospital we can be for our patients and families.”

ACOs still remain relatively rare concepts in pediatric care. Children’s Hospital Colorado doesn’t have an ACO other than a small pilot project with the state of Colorado, but Dr. Hyman predicts change is coming.

“ In an environment where costs are less likely to be reimbursed for preventable harm, harm prevention becomes not only the right thing to do for the patient but also the right thing to do economically. ”

— Daniel Hyman, MD, chief quality and patient safety officer for Children’s Hospital Colorado



“ The health care industry is about the only industry where you’re paid to hurt people. It sounds over the top, but it’s true. We get paid for things we do poorly. ”

– Richard McClead, MD, associate chief medical officer for Nationwide Children’s Hospital

“The vast majority of costs in our national health care system are in the adult world,” he says. “So we’re kind of the tail of the dog. But I think children’s hospitals are clearly doing the right thing by investing and testing approaches to global reimbursement and capitated contracts where there is alignment with the right care and lower costs and better outcomes.”

The Affordable Care Act encourages the creation of ACOs, which reward providers for keeping their patients healthy. “It’s becoming more and more the case that the whole country is going to have to go in this direction,” Dr. McClead says. “And they better get on board with finding out how to improve outcomes.”

THE FEEDING CHALLENGE

Around 2009, Dr. McClead began to explore how Nationwide Children’s could improve the quality of care in the neonatal intensive care unit. When he looked at the data, he discovered that 75 percent of similar children’s hospitals had shorter lengths of stay for babies admitted to their NICUs. “That was kind of a marker for the fact that we had a problem,” Dr. McClead says.



For extremely premature babies, feeding is a particularly complex challenge involving the brain, airway and foregut. What’s more, variable training, inexperienced personnel and lack of communication among NICU staff made feeding even more difficult. “The bottom line was there was inadequate knowledge being disseminated inadequately,” says Sudarshan Jadcherla, MD, principal investigator in the Center for Perinatal Research at Nationwide Children’s.

Dr. Jadcherla developed a standardized approach called SIMPLE (simplified, individualized, milestone-targeted, pragmatic, longitudinal and educational) to improve feeding in the Nationwide Children’s NICU. The program analyzes institutional processes, builds consensus, improves communication, monitors compliance and accountability and offers educational opportunities through workshops.

In a study published this year in the *Journal of Parenteral and Enteral Nutrition*, Dr. Jadcherla and his co-authors reported that the SIMPLE program shortened stays in the hospital’s NICU by as much as two weeks without any drop in the quality of care. “Much of the time the premature baby spends in the hospital is learning how to eat,” Dr. McClead says. “If we’re not very competent about how to accomplish that, then the kid’s going to be in the hospital longer. So what Dr. Jadcherla provided was that structure on how we approach feeding.”

The findings have generated much interest. The new approach can result in significant savings — each day of hospitalization in the NICU costs between \$2,000 and \$3,000, depending on the institution, Dr. Jadcherla

Dr. Sudarshan Jadcherla (top) and Dr. Richard McClead (bottom) are innovating ways to improve patient care and the bottom line through quality improvement initiatives.



says. Two other hospitals — Connecticut Children’s Medical Center in Hartford and MetroHealth System in Cleveland — are exploring implementing the program.

But it will take a lot of work to replicate Nationwide Children’s NICU success. It’s easy to imagine ideas that can hit the sweet spot of better care and better business, but it’s much more difficult to execute and deliver on the increasingly important goal. “It’s very challenging and very difficult to do this,” Dr. Jadcherla says, referring to the SIMPLE program. “It needs education. It needs commitment from the institution. And, of course, it needs the concerted approach of the NICU staff.”

A QUALITY FUTURE

With ACOs, quality improvement and preventable harm gaining the spotlight in health care, Drs. McClead, Jadcherla, Hyman and other pioneers are leading the way to merge better care and better business. Their work points toward a new future where forward-thinking leaders across the medical spectrum embrace improving outcomes and cutting costs as the traditional fee-for-service economic model goes away.

With health care in so much flux, Dr. McClead can’t help but wonder about the neonatologist he met in Boston five years ago and whether his hospital’s point of view has evolved since then. “I bet they’re far from, ‘Why are you doing that?’ ” he says.



Join the conversation. Visit PediatricsNationwide.org/Better-Care to weigh in on how hospitals can achieve both better care and better business.

REVEALING THE SECRETS OF SEPSIS

CHARTING NEW TERRITORY IN THE UNDERSTANDING OF HOW THE IMMUNE SYSTEM RESPONDS TO SEPSIS

..... by Abbie Roth

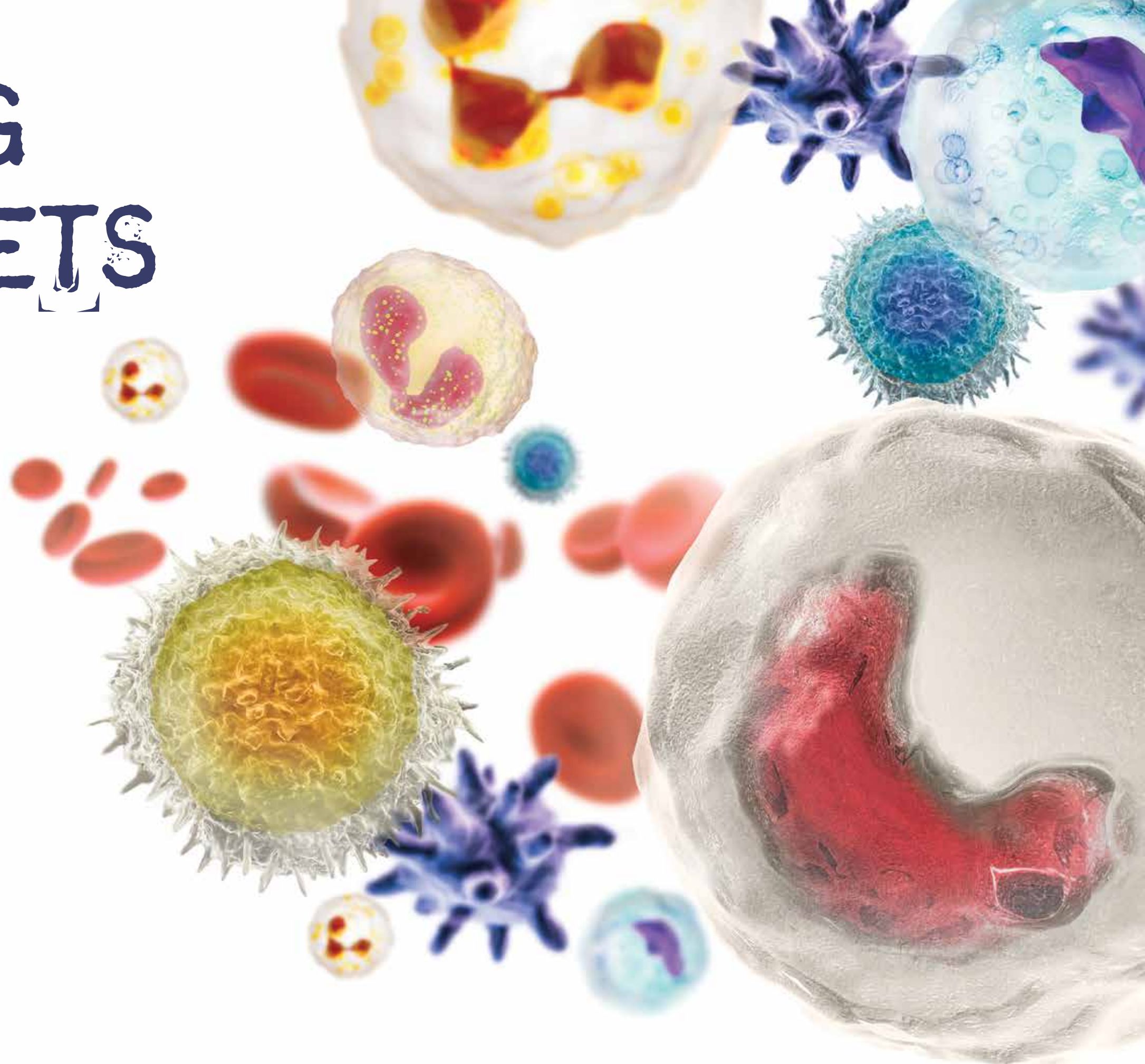
Two children are admitted to the hospital with sepsis. Both receive antibiotics and fluid resuscitation within the critical first hour. Why does one get better after the initial crisis while the other goes on to develop additional infections and multiple organ failure?

This is the question plaguing critical care doctors and researchers around the world. The answer is as complex as the immune system itself.

Traditionally, doctors and researchers have understood that the comorbidities and signs and symptoms associated with sepsis all stem from an overactive immune response. The fever, high respiratory rate, low blood pressure and low organ perfusion associated with severe sepsis are all the result of an out-of-control immune response being waged against an infection.

But this is not the whole story.

While the body is waging war on the infection, it is also sending in the peacekeepers, the anti-inflammatory mediators meant to calm the immune system



so that the body does not destroy itself. In a perfect situation, these two sides of the immune response to sepsis complement one another, defeating the initial infection, calming the overstimulated immune system and regaining homeostasis.

For some, however, homeostasis remains out of reach. Once the immune system is suppressed it stays suppressed and the patient is faced with nosocomial (hospital-acquired) infections, multiple organ failure and death.

The view that immunosuppression in the context of sepsis is real and is associated with poor outcomes is the result of 15 years of research that has caused a paradigm shift in research and critical illness care. Since the 1990s, researchers have been documenting and studying the phenomenon of immunoparalysis — extreme immunosuppression in the case of sepsis.

Critical care expert Dr. Mark Hall is leading the quest to solve the mystery of the immune response to critical illness in children by developing and refining tests to identify immunoparalysis and testing drugs to reverse it.

SEPSIS AND THE IMMUNE SYSTEM

“Sepsis is a systemic response to an overreaction of the immune system to an infection,” says Dr. Hall, principal investigator in the Center for Clinical and Translational Research in The Research Institute at Nationwide Children’s Hospital. “Over time, we evolved mechanisms for shutting down this

overreaction of the immune system — an ‘off switch’ to shut down the inflammatory response. But in some cases, the switch stays off, and the patients experience nosocomial infections with no ability to fight them.”

After the on switch is triggered, causing the immune cells to release pro-inflammatory mediators to fight the infection, the off switch is then thrown, causing other immune cells to release anti-inflammatory mediators. When the anti-inflammatory response takes over, it can promote resolution of the acute phase of sepsis. But when the switch stays off, the effect can be disastrous.

“Sepsis results in a more severe immune loss than does HIV infection,” says Richard Hotchkiss, MD, professor of Anesthesiology, Surgery and Medicine at Washington University School of Medicine. “When a patient has an active HIV infection, they’re losing CD4+ T-cells. When a patient is septic, they are losing CD4+ and CD8+ T-cells, B-cells, dendritic cells, monocytes — a whole host of immune cells.”

Studies done in the pediatric intensive care unit (PICU) setting are providing pathologic findings very similar to what are seen in adult patients, says Dr. Hotchkiss. Lymphocytes are massively depleted in sepsis patients, regardless of age. Additionally, the types of organisms that trigger nosocomial infections in the newborn ICU (NICU) and PICU are often not very virulent, providing secondary evidence that the immune system has been suppressed, he continues.

“Sepsis results in a more severe immune loss than does HIV infection. When a patient is septic, ...they are losing a whole host of immune cells.”

— Richard Hotchkiss, MD, professor of Anesthesiology, Surgery and Medicine at Washington University School of Medicine

UNINTENDED CONSEQUENCES OF CRITICAL CARE TREATMENTS

Beyond the immunosuppression caused by the immune system’s response to sepsis, a myriad of treatments provided in the ICU probably have unintended immunologic consequences, says Dr. Hall. Some medications, such as corticosteroids, transplant anti-rejection drugs and chemotherapy, are overtly immunosuppressive.

“Using anti-inflammatory medications in the setting of sepsis or other critical illness is something we need to think very carefully about,” says Jennifer Muszynski, MD, principal investigator in the Center for Clinical and Translational Research at The Research Institute. “It also needs to be the subject of ongoing research.”

Other drugs are usually considered benign when it comes to immune suppression — diuretics, sedatives, pain medication. But now, Drs. Hall and Muszynski believe these might also impair immune function.

“These medications are not used with the intent to modulate the immune system, but they likely are affecting it to some extent. We need to understand how much they are doing so,” Dr. Hall says. “Many critically ill patients are on a combination of all of these medications. Could the cumulative effect of these ‘benign’ medications impact the patient’s immune system in a way that affects outcomes? We don’t know yet, and we’re really just scratching the surface on our understanding of these relationships.”

In Dr. Muszynski’s lab, transfusion immunobiology is garnering attention as one area of research on the

unintended consequences of traditional therapies.

“By transfusing red blood cells in critically ill patients, are we unwittingly doing something to modulate the immune system?” she asks.

Intriguing evidence from her group and others so far suggests, “yes.”

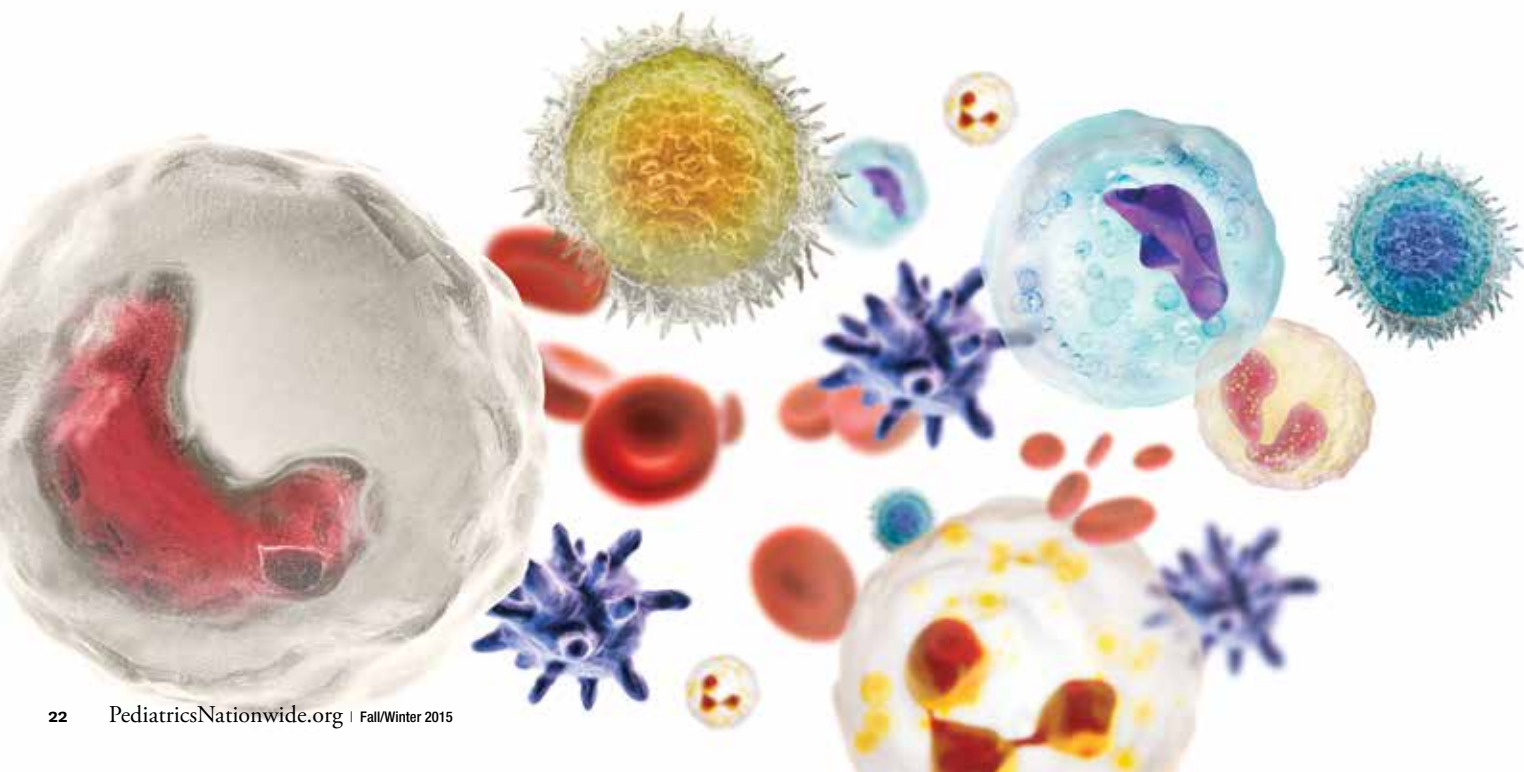
In both *in vitro* and *in vivo* studies in critically ill children, the results suggest the way the cells are stored and how long they are stored may be associated with a perpetuation of immunoparalysis. “The studies are smaller but quite intriguing,” Dr. Muszynski says. “We’re seeing the same thing at the bench and the bedside. Moving forward, we need to look at larger groups to identify and understand the risk factors.”

For Drs. Hall and Muszynski, the results so far are enough to influence the way they treat patients. “Though we still transfuse some patients, we don’t transfuse as often as we used to,” says Dr. Hall.

IDENTIFYING IMMUNOPARALYSIS

While they may not be able to predict who will become immunosuppressed or how each of the treatments offered in the ICU will impact the immune system of each patient, Drs. Hall and Muszynski use two relatively simple tests to determine whether or not a patient is suffering from immunoparalysis. They look beyond cell counts and standard blood tests to assess how well the immune system is working.

The first test measures HLA-DR expression on monocytes. HLA-DR is an important immune system cell surface protein that is normally present



on monocytes, but whose expression drops in the setting of immunoparalysis. The more HLA-DR the monocytes are expressing, the better the immune system is working, explains Dr. Hall.

“We stain whole blood and identify monocytes based on cell surface characteristics. Then we run the sample through a flow cytometer to quantitate the degree of expression of HLA-DR,” says Dr. Hall. “Thresholds have been identified below which patients are ostensibly at risk.”

The second test — the doctors’ preferred test — measures *ex vivo* LPS-induced TNF-alpha production capacity. TNF-alpha is a pro-inflammatory cytokine produced by monocytes. Lipopolysaccharide (LPS) — also known as endotoxin — induces an inflammatory response when it is mixed with blood cells. Sampled blood is mixed with LPS to induce cytokine production. Then, the amount of TNF-alpha produced is quantified using chemiluminescence.

“We have found over and over in single- and multicenter work in a wide variety of critical illness phenotypes in children that suppression of TNF production capacity is a bad thing, and severe suppression is a terrible thing with markedly increased risks for developing secondary infection and death,” says Dr. Hall.

The team at Nationwide Children’s has standardized their approach such that they now manufacture kits and send them to other institutions for multicenter work. “In one such study underway this summer, participating teams collect samples and ship the

tests back to us overnight so that we can provide near-real-time information to drive therapy over the course of the study,” Dr. Hall says.

From a single-center perspective, Dr. Hall says, these are very feasible and high throughput tests. “For example, if we get a blood sample at 8 a.m., we can have results by 2 p.m.,” he explains. “This is very fast compared to traditional immune function tests.”

“Our work is not just about the lab. We are directly connected to the PICU,” says Dr. Hall. “In fact, we recently had a small lab for our work built on the PICU floor. This brings the tests needed for identifying immunosuppression literally steps away from the bedside. The faster we can identify immunosuppression, the faster we can begin using strategies to reverse it.”

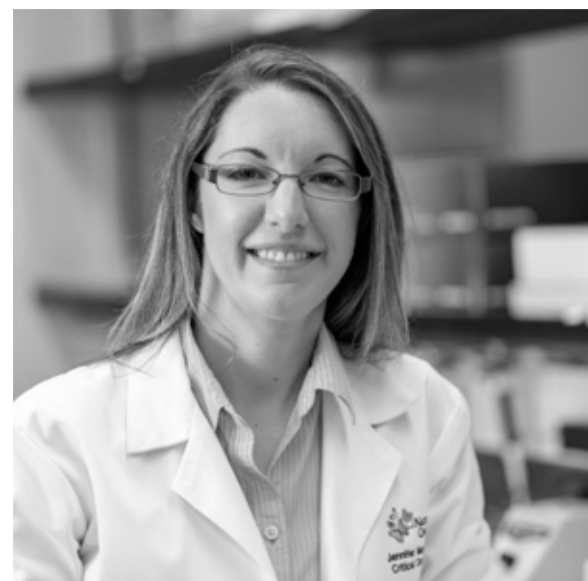
TNF-alpha production capacity and HLA-DR expression form a nucleus of immune function testing that is missing from the clinical laboratory. “Our hope is that over time, using data we and others are collecting, these tests will move to the clinic and be used routinely,” Dr. Hall says.

This type of critical illness-induced immune suppression can, and does, occur in many types of critical illness. “As we show that this testing and intervention works, we can make the testing part of the routine workup,” says Dr. Hall.

“We think it’s particularly important to identify immunosuppression not only in septic infections but to prevent hospital-acquired sepsis,” Dr. Hall says. In the case of critically ill patients without sepsis, such as those recovering from trauma, early identification of

“We want to put things into nice little boxes — adaptive, innate — only to realize that those boxes don’t really exist, and it’s a bit more complex than that.”

— Jennifer Muszynski, MD, principal investigator in the Center for Clinical and Translational Research



Through their research, Dr. Jennifer Muszynski (left) and Dr. Mark Hall (right) are advancing the understanding of the immune response to critical illness and testing targets for new therapies.

immunoparalysis could help the medical team prevent infections that could lead to sepsis.

Identifying patients with immunoparalysis is just the beginning. Dr. Hall and his contemporaries believe that once identified, these patients can be helped by using drugs to boost their immune systems.

INNATE OR ADAPTIVE?

The two branches of the immune system, the innate and adaptive arms, are intricately intertwined. Though the cells of each branch have different targets, they are both critical to defending the body against infection. The innate immune system refers to monocytes, neutrophils, and the other nonspecific defense mechanisms that defend the body immediately, while the adaptive arm refers to lymphocytes, T-cells and B-cells, which are stimulated by signal cascades produced by the innate immune system to produce antigen-specific attacks.

In such a complex system, determining where to target therapies that boost immunity is not a simple task. “We think that if you stimulate the innate arm of the immune system, the rest of the immune cells will come along,” says Dr. Hall, who is also associate professor of

Pediatrics, Division of Critical Care Medicine at The Ohio State University College of Medicine. “However, we understand that multiple approaches to immune-system stimulation are likely to be optimal. It may also be true that you need to target both sides of the immune system to get optimal results.”

Drs. Hall and Muszynski are testing this hypothesis through numerous studies. In a small cohort, Dr. Muszynski looked at immune function in both arms of the immune system. She found that while septic children overall showed evidence of both innate and adaptive immune suppression, those children who went on to develop persistent infections or new nosocomial infections had a suppressed adaptive immune system as measured by T-cell cytokine production. “We want to put things into nice little boxes — adaptive, innate — only to realize that those boxes don’t really exist, and it’s a bit more complex than that,” Dr. Muszynski says.

Dr. Hotchkiss agrees, “You can’t neatly separate the function of the two arms of the immune system.” But you do have to choose a target for therapies.

Dr. Hotchkiss’ work more directly targets the adaptive immune system by focusing on lymphocytes.

“The greatest area for growth potential is the interventional arm of our research. We believe immunoparalysis is reversible through drug treatment. And reversal will hopefully improve outcomes.”

— Mark Hall MD, division chief for Pediatric Critical Care Medicine

“Lymphocytes are master regulators of the immune cells,” he explains. “They are critical in controlling many facets of immunity. If you don’t get the CD4+ and CD8+ T-cells working, the other components are trying to function like they have one arm tied behind their back.”

REVERSING IMMUNOPARALYSIS

The mainstay for treatments for sepsis at this point is twofold: the prompt response to shock when it exists and prompt and accurate administration of antibiotics. “We’ve gotten pretty good treating the acute phase of sepsis,” says Dr. Muszynski. “Quality measures are underway to improve this further, but overall, we’re doing pretty well in that area.”

When it comes to immunoparalysis during the subacute phase of sepsis, however, the therapies with the most promise for treating immunoparalysis are not approved or available to patients.

“The greatest area for growth potential is the interventional arm of our research,” Dr. Hall says. “We believe immunoparalysis is reversible through drug treatment. And reversal will hopefully improve outcomes.”

Dr. Hall’s drug of choice for reversing immunoparalysis is granulocyte macrophage colony-stimulating factor (GM-CSF), a drug commonly used to treat neutropenia following chemotherapy. GM-CSF functions as a

cytokine and stimulates the production of neutrophils and monocytes and also improves the function of immunoparalyzed innate immune cells.

In a small (14 patient) study, Dr. Hall and his team showed that patients who received GM-CSF showed immunoparalysis reversibility, had better outcomes and did not develop new infections.

“We have been working to evaluate GM-CSF as an immunostimulant in selected patients ever since,” says Dr. Hall, who is currently leading a clinical trial of the drug to prevent hospital-acquired sepsis in trauma patients.

Dr. Hotchkiss’ interventional work focuses on Interleukin-7 (IL-7), a drug that has been tested in more than 300 cancer and HIV+ patients to increase the number and activity of lymphocytes.

“IL-7 prevents cell death and promotes the proliferation of T-cells,” Dr. Hotchkiss says. “It has been effective with viral infections and shown some activity in cancer patients. This is an exciting drug and we’re going to see lots of trials with it in the future.”

Regardless which drug is being used, perhaps the biggest challenge in using drugs to modulate the immune system is getting the medications to the right patients.

“You might imagine that if you gave a drug to a whole bunch of people, only about half of whom actually needed it, then you’d be highly unlikely to see an effect

Through his work to describe and understand the immune system’s response to sepsis, Dr. Richard Hotchkiss has contributed to the shifting paradigm in the field.



of the drug on outcomes,” explains Dr. Hall of the mixed results immunomodulation has presented thus far. “Our approach is an individualized medicine approach.”

Dr. Hotchkiss agrees GM-CSF will likely have a role in treating immunosuppression in sepsis. “It hasn’t had great success in trials so far, but before we were giving it to everyone. Now that you can target immunosuppressed patients, the hope is that the right patients are getting the right drug and you’ll see better outcomes,” he explains.

PREDICTING THE FUTURE

Identifying and treating immunoparalysis in patients with sepsis and other critical illnesses will have a dramatic effect on outcomes for these patients.

But what if researchers can take it one step further? What if they could determine who is likely to go down the immunoparalysis pathway at the onset of their illness?

This is a direction for future research in this field.

“What predisposes patients to immune suppression? Is it the disease the patient came in with, is it the patient’s genetics? We don’t know,” says Dr. Hall. “A vast

number of influences are acting on the patient at any point during his or her illness. It is difficult to predict who will go down the immunosuppression pathway.”

Other researchers in the field are working on just that. Dr. Hector Wong at Cincinnati Children’s Hospital Medical Center and his team are using genomic and

proteomic biomarkers to predict which sepsis patients are likely to do well and which ones are likely to do poorly. According to Dr. Hall, a natural extension of this work would be to look for markers that predict sepsis phenotypes, including immunoparalysis.”

“Discovering how the individual host immune response contributes to differences in outcomes and how we can tailor our treatments to those differences is the next frontier in sepsis research,” Dr. Muszynski says.



Join the conversation. In light of increasing evidence that therapies used to treat critical illness may contribute to immunosuppression, what are the next steps to consider? Lend us your voice at PediatricsNationwide.org/Secrets-of-Sepsis.



THE TRANSFUSION EVOLUTION

How Strategies to Reduce Transfusions are Changing Cardiothoracic Surgery

..... by Abbie Roth

The first successful open heart surgery with cardiopulmonary bypass was performed in 1953, but it wasn't until the 1970s that these surgeries began to have high success rates — due in large part to the availability of fresh whole blood transfusions.

However, fresh whole blood is difficult to attain. In response, blood component transfusions became a more popular solution. As techniques for administering blood components improved, physicians reaped the added benefit of giving patients only the components they needed.

Now, the evolution of cardiothoracic surgery and transfusion medicine continues with advances in surgery, anesthesiology and perfusion, ushering in a new era in which whole and component blood transfusions may become a thing of the past.

Undoubtedly, blood and blood product transfusions save lives. But while blood transfusions are much safer now, inherent risks are still associated with using donated blood products, including allergic reaction, infection and increased edema and inflammation.

Furthermore, the availability of allogeneic blood products is not guaranteed. According to the American Red Cross, more than 41,000 blood donations are needed every day and 300 million blood components are transfused each year in the United States. Conventional wisdom emphasizes limiting the use of blood products. However, how to safely achieve that goal during pediatric cardiac surgery is still up for debate.

Chief of Cardiothoracic Surgery Mark Galantowicz, MD, and his team in The Heart Center at Nationwide Children's Hospital are challenging the culture of transfusion with new techniques and aggressive strategies of blood conservation for all their patients.

PHILOSOPHY OF CELL SALVAGE

One technique used with great success at The Heart Center is cell salvage — saving blood that is shed or removed from the body so that it can be reintroduced to the patient. And it's more than a technique, it's a philosophy. "We look for places to conserve the patient's own blood inside and outside the operating room," says Dr. Galantowicz. "For example, when you draw a blood sample from an IV, some blood diluted with saline or medicine is extracted before the clean sample is drawn. Usually, the diluted blood is just thrown away, but we give it back to the patient. It just takes a little time and effort to make this change."

The same is true for blood that is left in the bypass circuit once surgery is complete. Many institutions dispose of this blood without attempting to give it back to the patients. However, with the use of a cell saver machine, this blood can be safely cleaned and given as an autologous transfusion.

Central to the cell salvage philosophy is the intraoperative use of a cell saver machine to collect, clean and return shed blood back to the patient. The blood collected can be given back continuously or saved for post-operative autologous transfusion.

"Some people argue that with intraoperative cell salvage, too little blood can be collected during pediatric surgery to make it worthwhile," says Ashley Hodge, MBA, CCP, FPP, cardiothoracic surgery quality and safety officer and perfusionist with The Heart Center. "Our nurses are vigilant about collecting blood that is lost — besides using suction, they rinse and wring out sponges and gauze pads."

Another misconception about cell salvage relates to the safety and functionality of the red cells collected via intraoperative cell salvage. "Historically, it was believed that you couldn't safely capture shed blood and that the red cells wouldn't work properly when readministered. But this has been shown to be incorrect," says Dr. Galantowicz, who is co-director of The Heart Center.

“It’s a combination of a lot of small changes that work together to make a really big difference in the outcome.”

— Mark Galantowicz, MD, co-director of The Heart Center

The cell saver machine is also used to wash donor blood when a transfusion is needed. “Donor blood is high in glucose, high in potassium and high in lactate. All of these things can have negative effects on the patient, including arrhythmias, kidney problems, prolonged vent times and infections,” notes Joseph Timpa, CCP, FPP, chief perfusion manager and ECMO co-coordinator at Children’s of Alabama. “Washing donor blood with a cell saver helps prevent these conditions.”

According to Dr. Galantowicz, the initial cost of the cell saver machine and the disposable component that is replaced for each surgery is well worth it. “When you compare it to the cost of donor blood and the benefit to the patient and the shortened length of stay, it pays for itself,” Dr. Galantowicz says.

HONING IN ON HEMODILUTION

Hemodilution — diluting red cell concentration in the blood — is one of the major factors to be managed during cardiopulmonary bypass, according to Dr. Galantowicz, who also is professor of Surgery at The Ohio State University College of Medicine. Several strategies to limit hemodilution are required for a surgical course free of allogenic blood products. “It’s a combination of a lot of small changes that work together to make a really big difference in the outcome,” he explains.

By reducing the size of the cardiopulmonary bypass (CPB) circuit, a smaller volume of blood is in the circuit at any given time, leaving more blood in the patient. As an added benefit, miniaturized circuits decrease inflammation that results from the blood cells reacting to the foreign material of the CPB circuit.

“We use many different circuit sizes for cardiopulmonary bypass to more closely match the circuit size to the body weight of the patient,” explains Dr. Galantowicz.

Additional whole-team strategies to limit hemodilution and reduce the need for donor blood products are applied before, during and after bypass:

- Before bypass is initiated, retrograde autologous prime and venous antegrade prime (RAP and VAP) procedures are attempted with each patient. These procedures involve displacing the crystalloid in the CPB circuit by back-bleeding the patient’s own blood into the circuit.
- During bypass, hemofiltration and zero-balance ultrafiltration (ZBUF) extract various inflammatory markers.
- After bypass, modified ultrafiltration (MUF) is used for hemoconcentration and removal of inflammatory progenitors.

In addition, vacuum-assisted venous draining (VAVD) is a strategy that Timpa and his team at Children’s Hospital of Alabama use to aid in blood conservation. “Without VAVD, drainage is dependent on gravity and a height differential from the patient to the cardiotomy reservoir,” explains Timpa. “By using VAVD, the perfusionist can decrease the tubing length even more, which translates to reduced prime volume and hemodilution.” VAVD also enables surgeons to use smaller cannulae without compromising flow.

ANH RESULTS IN FEWER TRANSFUSIONS

One of the most innovative strategies that The Heart Center team utilizes is acute normovolemic hemodilution (ANH), a process in which a percentage of the



Nurses carefully suction blood during surgery. This blood is cycled through the cell saver and returned to the patient.

total blood volume is withdrawn prior to bypass and returned to the patient after heparin reversal. In a research study published earlier this year, this process was associated with a decreased number of transfusions.

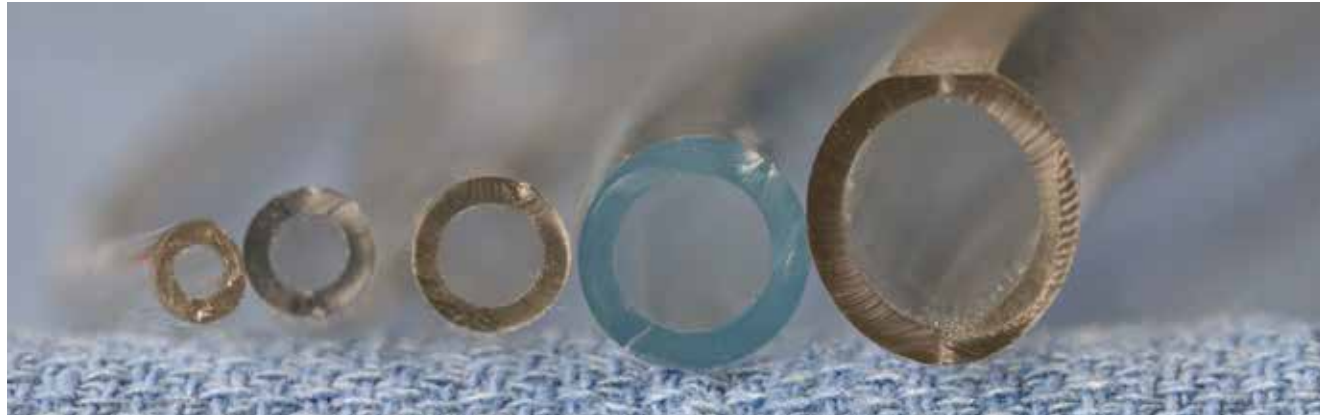
According to Hodge, ANH is attempted in about 90 percent of heart surgeries at Nationwide Children’s.

“Our process of ANH is novel,” she says. “Many people are surprised that we are able to take so much volume — up to 20 percent — at the start.”

“Our practice of ANH is unique in that we minimize crystalloid replacement during phlebotomy and use end-organ perfusion to guide fluid replacement,” Dr. Galantowicz explains. “Additionally, the blood collected during ANH has more intact platelets and fewer inflammatory markers because it does not circulate through the CPB circuit. This strengthens the patient’s ability to heal.”

“ANH is really good at minimizing blood exposure,” says Timpa.

In traditional practices, all that extra volume from crystalloids leads to worsening edema after surgery, but the difference in post-surgical results for The Heart Center’s strategy is immediately evident. “Our patients aren’t as puffy when they come out of surgery. They



To limit the volume of blood in the bypass machine, different diameters of tubing are used depending on the size of the patient. The diameters range from 1/8 inch to 1/2 inch.



look like the same kid that came in to the operating room,” explains Hodge. “We are even able to extubate most patients immediately after surgery in the OR — that’s unheard of in most institutions.”

HOW LOW CAN YOU GO?

Determining the lowest acceptable hematocrit — the amount of hemoglobin in the blood — remains a complex challenge. “There is this ‘religion’ of finding the perfect hematocrit for bypass that will give you the best outcomes every time,” says Timpa. “But the research regarding the hematocrit needed for successful heart surgeries is confirming that lower numbers than previously thought are acceptable.”

The role of the hemoglobin is to deliver oxygen to the cells, tissues and organs of the body. And the amount of hematocrit that is adequate is completely dependent on oxygen demand, explains Dr. Galantowicz. Oxygen demand is variable: it depends on the tissue type, cardiac output, body temperature and activity level.

But most surgeons and families want a concrete number.

“There is no number,” Dr. Galantowicz emphasizes. “An absolute number would be based on the partial pressure of oxygen needed to move the oxygen from the hemoglobin in the blood to the mitochondria in the organs’ cells, but this number is also fluid, so it’s debated.”

Dr. Mark Galantowicz (top) and perfusionist Ashley Hodge (bottom) work with the whole team to minimize the number of transfusions needed for their patients.

“ Blood exposure is a risk that people don’t pay attention to as often as they should when faced with surgery. ”

— Joseph Timpa, chief perfusion manager at Children’s of Alabama

According to Dr. Galantowicz, the best way to determine if the organs are getting enough oxygen is to monitor them. “We use blood tests to monitor lactate and blood gases. We monitor the brain, kidneys, liver, heart and total body perfusion during and after surgery,” he says. When oxygen delivery is in danger of becoming inadequate, the team addresses cardiac output and oxygen demand, and, if needed, transfuses red cells to boost hematocrit.

A CULTURE OF CONSERVATION

As with the conservation of any resource, blood conservation requires education, advanced technologies, innovation and behavioral change.

The first step is awareness. “Blood exposure is a risk that people don’t pay attention to as often as they should when faced with surgery,” says Timpa. “We need to work to find better ways to reduce blood exposure where we can, and educate physicians and families about the risks, benefits and options when it comes to blood conservation.”

The movement is slowly gaining traction. With innovations in blood conservation, new research into blood substitutes and education about these topics, surgical and transfusion medicine continues to mature. “In the relatively short history of open heart surgery with cardiopulmonary bypass, we’ve seen great advances,” says Hodge. “Aggressive yet safe blood conservation will be central to moving the field forward.”

“We are evolving a fuller understanding of the pros and cons of transfusion,” Dr. Galantowicz says. “Blood is life-giving, but at a cost. We need to continue to work to capture more of the benefits and reduce the risks.”



Blood Conservation and Religion

Advocating “bloodless surgery” on religious grounds has been a significant factor leading to the current state of blood conservation. Many of the innovations used for blood conservation were driven by surgeons working to meet the needs of patients and families who are Jehovah’s Witnesses.

These techniques may often be overlooked and disregarded, though, as simply putting children in harm’s way to accommodate certain belief systems.

“Many families choose Nationwide Children’s Hospital because of our history with aggressive blood conservation,” Dr. Galantowicz says. “However, the procedures and limits used for children of Jehovah’s Witnesses families are no more aggressive than those used for every other child.”

When a child needs blood products, they get blood products.



Join the conversation. Visit PediatricsNationwide.org/Transfusion-Evolution to share your thoughts about blood conservation for pediatric surgeries.

Restoring Normal Habits

Sacral nerve stimulation helps school-age and teenage children control urinary incontinence and fecal soiling.

Sacral nerve stimulation (SNS) is a new treatment that helps control urinary incontinence and fecal soiling. For some children, the nerves that control urination and bowel movements do not work correctly. The SNS unit consists of a small, safe battery and wire under the skin and sends signals to the sacral nerve. The signals help restore

normal function and prevent accidents. SNS can be used on school-age and teenage children after other treatments have failed. If the medical team determines SNS is appropriate treatment, a two-part procedure is required to place the SNS unit under the skin.

Benefits of SNS

- Hold in urine
- Urinate fewer times a day
- Stop urine from leaking during the day
- Hold in bowel movements
- Relieve constipation
- Do normal, everyday activities
- Wear normal underwear
- Have more confidence

SNS and Pediatrics

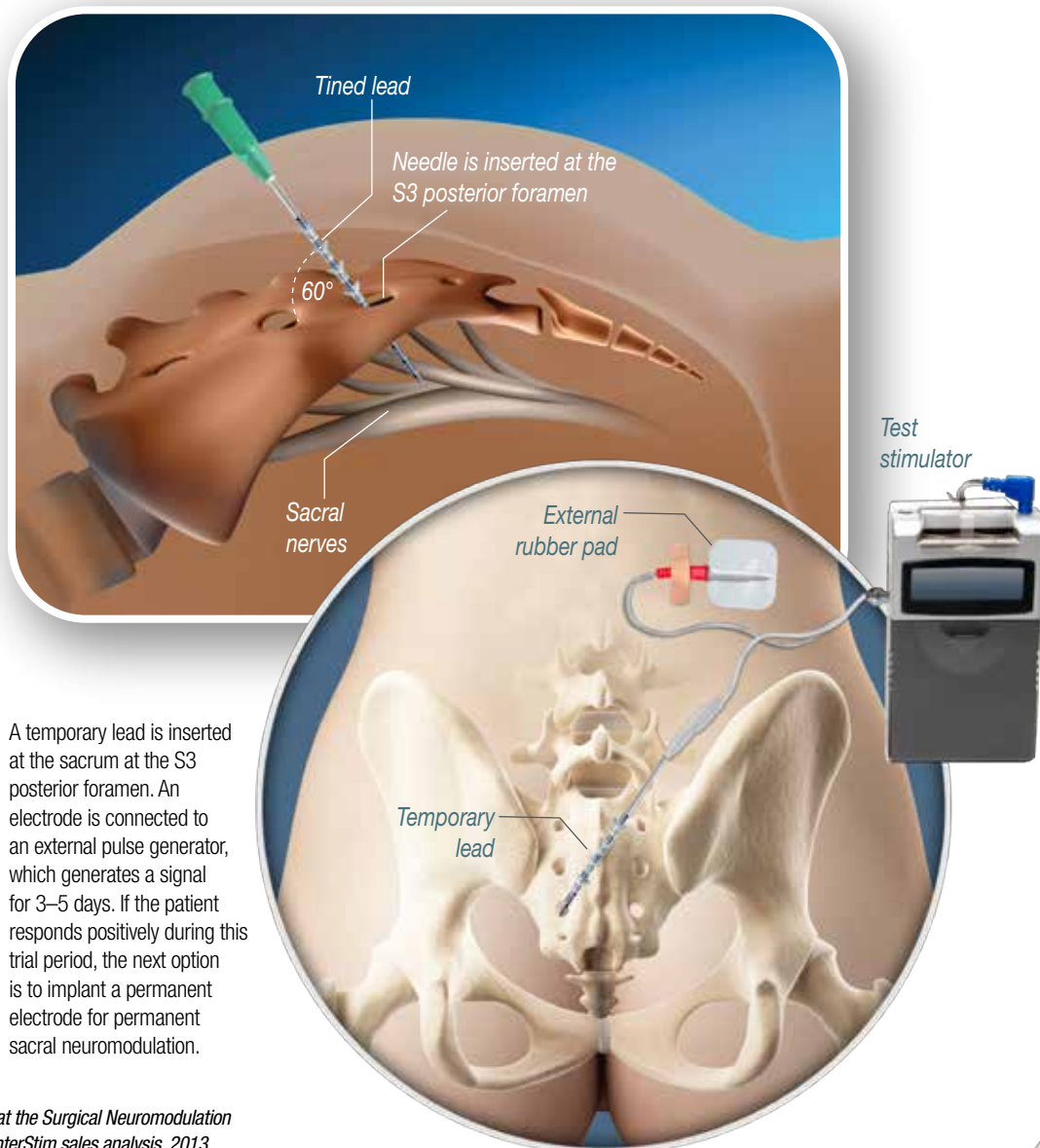
In the United States, several hundred pediatric patients have undergone sacral neuromodulation for bladder and/or bowel control.

Since 2012, Nationwide Children's Hospital has performed more than 60 of these procedures in pediatric patients.

Sources: Seth A. Alpert, MD, co-director at the Surgical Neuromodulation Center, Nationwide Children's Hospital; InterStim sales analysis, 2013
Graphic by: Christina Ullman, Ullman Design

1 The Trial Stimulator

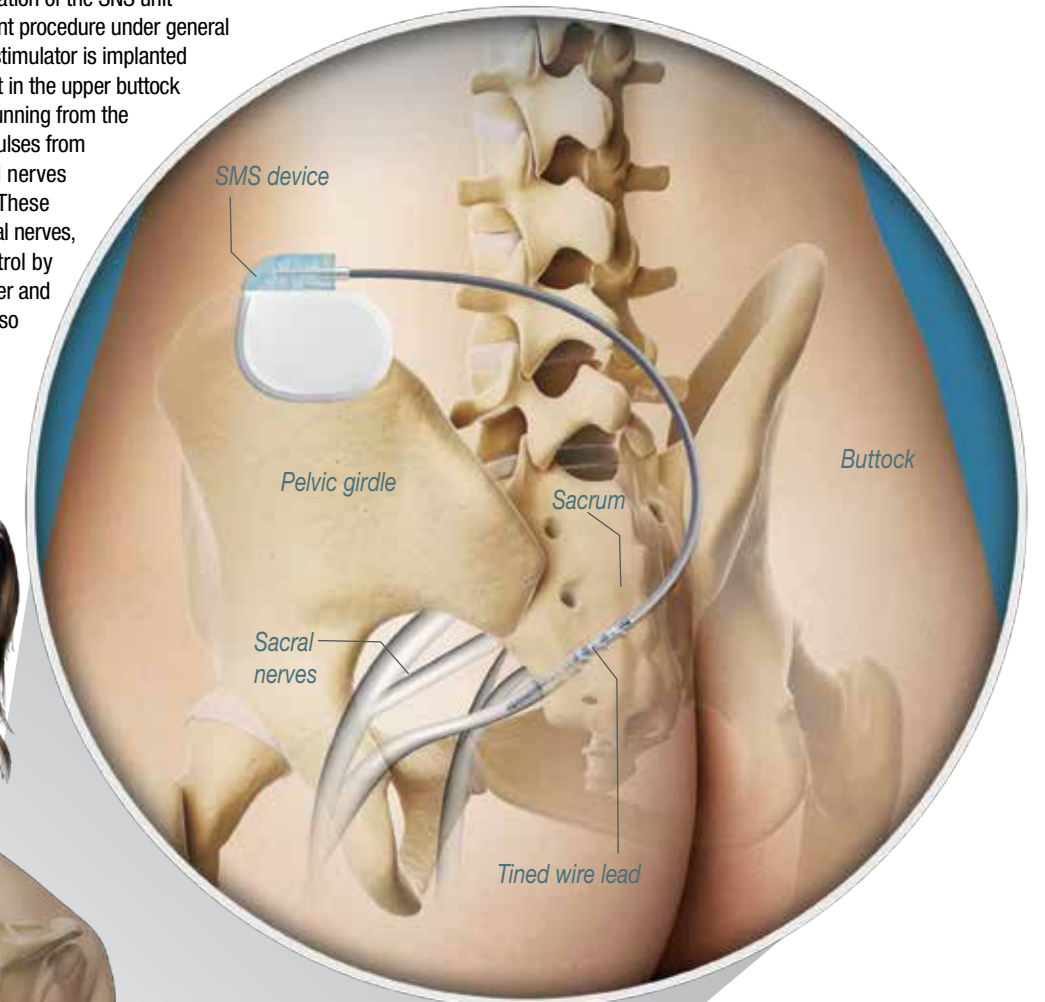
First, the physician/surgeon performs a trial to ensure SNS will work for the patient before placing a permanent stimulator. This procedure is done in an outpatient surgery setting under general anesthesia along with local anesthesia for additional pain control.



A temporary lead is inserted at the sacrum at the S3 posterior foramen. An electrode is connected to an external pulse generator, which generates a signal for 3–5 days. If the patient responds positively during this trial period, the next option is to implant a permanent electrode for permanent sacral neuromodulation.

2 The Permanent Stimulator

Permanent surgical implantation of the SNS unit is performed as an outpatient procedure under general anesthesia. The SNS neurostimulator is implanted under the skin of the patient in the upper buttock area. Thin wires, or leads, running from the stimulator to the sacral nerves located in the lower back. These impulses influence the sacral nerves, which provide bladder control by altering the bladder sphincter and pelvic floor muscles. SNS also improves bowel control by reducing fecal incontinence and constipation.

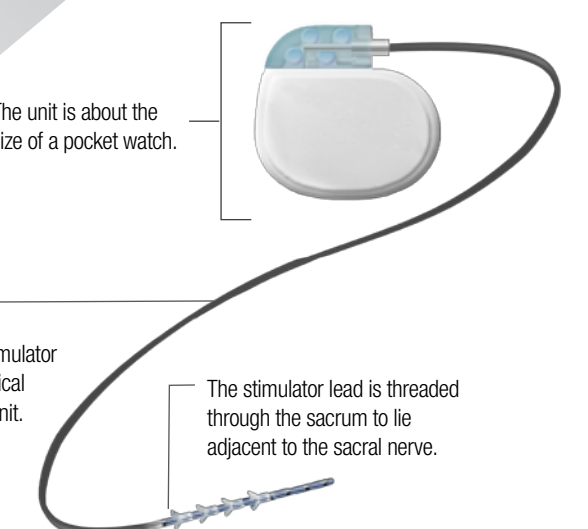


The SNS Unit

The unit is about the size of a pocket watch.

The sacral nerve stimulator lead transfers electrical impulses from the unit.

The stimulator lead is threaded through the sacrum to lie adjacent to the sacral nerve.



Second Opinions

Q: Studies have shown gender bias in nearly all aspects of work in academic and medical research institutions. How can institutions address and correct these biases and what are the costs of failures to do so?



A: Claims of gender bias in hiring, promotion, and remuneration are so ingrained that university policies are predicated on combating it. But is this view currently valid? We and our colleagues documented that some gender differences exist that benefit male scientists; however, the academic landscape is changing rapidly, and women and men are now treated comparably in most domains.

Four decades ago, women accounted for less than 1 percent of professors in academic engineering. Today they represent roughly 25 percent of assistant professors, and given comparable promotion and tenure rates, numbers of female senior professors should increase. Similar growth of women scientists over the past 40 years is seen in all traditional male domains – physics, chemistry, geosciences, mathematics and economics. More women focus on life sciences, humanities and social sciences, and among those who earn PhDs in these fields, women are less likely than men to apply for tenure-track academic jobs. However, when women do apply they are offered jobs at a higher rate: In five experiments, we demonstrated that 872 faculty members at 371 institutions

preferred to hire a woman over an identically-qualified man. These findings are supported by hiring data, which show women who apply for academic posts are advantaged over men.

– Stephen Ceci, PhD
Helen L. Carr Professor of Developmental Psychology
College of Human Ecology
Cornell University

– Wendy M. Williams, PhD
Professor and Director, Cornell Institute for Women in Science
Department of Human Development
Cornell University



A: Unfortunately, we're having the same conversations about the advancement of women in academic medicine that we had 25 years ago. I have had the unique opportunity to understand this issue as my husband also works in pediatric academic medicine. Over the years, I've witnessed countless examples of workplace gender inequity. The majority did not appear intentional, but that does not make it acceptable. Historically, I remained silent for as much as gender bias held me back it helped him advance, which was good for our family.

A solution needs to be aggressive and will not be easy. Women have unique workplace pressures that result in significant attrition. It is difficult for any individual to work 70 hours per week and appropriately care for their families. Round-the-clock and sick daycare need to be easily available. Meetings frequently start at 7 a.m. or 5 p.m. — hours that are hard on young families. Additionally, there is a shortage of female mentors for women starting their careers. Senior women need to be encouraged to give back.

Women must become outspoken voices for change. They must not fear the consequences of speaking out, only the consequences of remaining silent.

– Linda H. Cripe, MD
Pediatric Cardiologist, The Heart Center at Nationwide Children's Hospital
Professor of Pediatrics, The Ohio State University College of Medicine



A: Anything that explicitly or implicitly constrains women from full participation and advancement means that only half the talent pool has the opportunity to solve problems facing health and biomedical sciences. To address and correct the impact of gender bias, institutions should recognize that stereotypes about men and women have deeply rooted, powerful and generally invisible effects on how we interpret and evaluate information from men and women and on our own behaviors.

Several steps institutions can take include: (1) Make gender equity a visible priority. (2) Help all organization members realize the pervasiveness of the problem, acknowledge we all contribute to its perpetuation and that addressing gender bias requires ongoing commitment, vigilance and action. (3) Ensure pay equity by undertaking intermittent exercises that identify systematic pay differences and install triggers for automatic reviews. (4) Convene groups of women within departments and hear their issues. (5) In descriptors for positions or awards, use specific language, such as “an investigator who has held an R01” rather than “independent investigator” or other terms that may favor men. (6) To select leaders, implement search and screen committee processes and review institutional awards, endowed chairs, speakers lists, etc. to ensure women are included in appropriate numbers.

Approaching gender bias as a habit is a useful strategy. As with other unwanted habitual behaviors such as smoking, breaking the gender bias habit is a multistage process.

– Molly Carnes, MD, MS
Professor, Departments of Medicine, Psychiatry, and Industrial & Systems Engineering
Director, Center for Women's Health Research
Co-Director, Women in Science and Engineering Leadership Institute (WISELI)
University of Wisconsin-Madison



A: By 2012, 57 percent of U.S. pediatricians and 73 percent of pediatric residents were women; yet, pay disparities between women and men persist, and women continue to be underrepresented in academic leadership. No institution that fails to support and foster the career development of more than half of its professional members can have any hope of achieving preeminence.

Change requires leadership. Ensuring that hiring and compensation policies and practices are applied equally is a basic issue of fairness. Promotion and tenure policies must provide flexibility to accommodate work-life balance challenges and non-traditional career paths women sometimes follow, with a clear acknowledgement that both genders contribute to any vibrant institution. In 2009, the Department of Pediatrics at Baylor College of Medicine and Texas Children's Hospital had 590 faculty members, but never a woman chair or vice chair. Through a conscious effort to diversify leadership ranks, the department now has 1,093 faculty members and 10 vice chairs, seven of them women.

We are on the cusp of a golden age of innovation that will transform pediatric health care worldwide, driven largely by the women in residency training programs and junior faculty ranks today. The privilege of leading this transformation will fall to institutions that value and embrace workforce diversity at every level.

– Mark W. Kline, MD
Physician-in-Chief, Texas Children's Hospital
J.S. Abercrombie Professor and Chairman, Ralph D. Feigin Chair, Department of Pediatrics
Baylor College of Medicine



Join the conversation about gender bias. Lend us your voice at PediatricsNationwide.org/Gender-Bias.

Help us advance the conversation on child health.



Follow *Pediatrics Nationwide* on Twitter @NCHforDocs to stay up-to-date on pediatric research, clinical advances, practice tools, case studies, patient education and live tweets from professional conferences. Join the community of physicians and health care providers dedicated to advancing the conversation on child health.

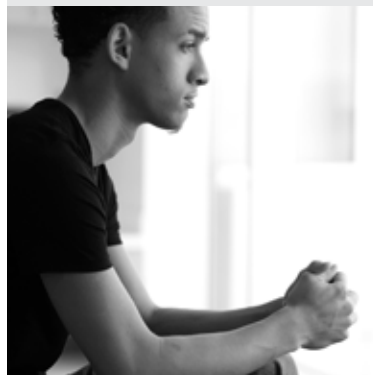
Join the conversation. Visit PediatricsNationwide.org for exclusive online content, physician commentaries and more.



Same Life-Threatening Diagnosis, Different Parental Wishes

by *Jeb Phillips*

Two infants in the same NICU face tracheostomy, months or years of chronic mechanical ventilation and future surgery. One family wants every intervention; the second family wants end-of-life comfort care only. How should a medical care team respond? Read more about this and other ethical issues in pediatrics at PediatricsNationwide.org/Parental-Wishes.



Challenges of Adolescent and Young Adult Cancer

by *Anthony Audino, MD, and Nicholas Yeager, MD*

Among the unique challenges of AYA cancer — increasing rates of diagnosis, survival plateau and psychosocial considerations — anxiety often increases after treatments are completed as the patient reintegrates back into “normal life.” Read more about issues affecting adolescents and young adults with cancer at PediatricsNationwide.org/AYA-Cancer.



Delayed Clamping and High-Risk Infants

by *Jeb Phillips*

Waiting a specific amount of time after birth to clamp the umbilical cord has advantages for newborns, but it is unclear if the practice is safe for some in the high-risk category. Recent research from Nationwide Children’s suggests that both extremely preterm infants and infants with critical congenital heart disease can benefit from delayed clamping. Visit PediatricsNationwide.org/Delayed-Clamping to read how Nationwide Children’s neonatologist and cardiologist Carl Backes, MD, is advancing perinatal care.

“Be curious, not judgmental.”

– Walt Whitman

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Publishers
Jan Arthur
Tonya Lawson-Howard

Editor/Writer
Abbie Roth

Staff Writers
Tiasha Letostak
Jeb Phillips

Contributing Writers
Dave Ghose
Kevin Mayhood

Art Director and Designer
Tanya Burgess Bender

Photographers
Brad Smith
Dan Smith

Illustrator
Christina Ullman

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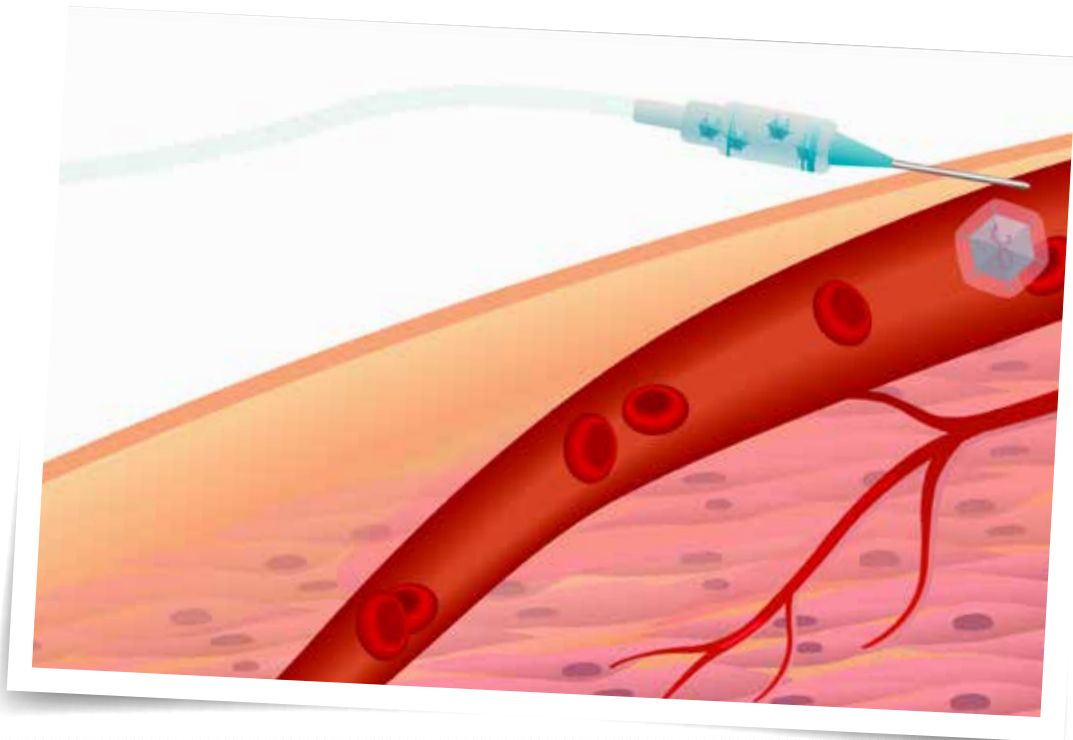


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Visualizing Gene Therapy for SMA

Spinal muscular atrophy (SMA), a degenerative neuromuscular disease, is the most common genetic cause of death for infants. Virtually all children affected with SMA type 1 die by 2 years of age. In 2014, Jerry Mendell, MD, director of the Center for Gene Therapy in The Research Institute at Nationwide Children's Hospital, began a phase 1 gene transfer clinical trial for SMA type 1. In this trial, a large number of modified viruses containing the missing SMN1 gene are administered to the patient. By administering the gene early in the disease process, the team hopes to effectively halt the progression of the disease.

To learn more and watch a video about the SMA1 clinical trial, visit PediatricsNationwide.org/SMA-Trial.