CookChildren's

Cook Children's Hyperinsulinism Center

Dear friends and colleagues,

It is my privilege to present Cook Children's Hyperinsulinism Center, one of only two of its kind in the country. At Cook Children's, our congenital hyperinsulinism (HI) team is dedicated to providing the very best care to patients and families facing this rare diagnosis.

In the past, saying the word 'cure' in relation to HI was only a dream. Now that we can offer the investigational new drug 18F DOPA combined with a PET-CT scan to more accurately diagnose and treat HI, a cure has become a reality.

As one of the premier programs in the country, we have built a world-renowned team that's devoted to providing quality, family-centered care to the children we serve. We offer access to a highly skilled, multidisciplinary team of physicians specializing in Endocrinology, Pediatric Surgery, Neonatology, Neurology, Gastroenterology, Pathology and Radiology. Our team is supported by a dedicated HI nurse practitioner, social worker, clinical therapist, child life specialist, nutritionists and feeding and speech therapists. This team works closely with patients and families to provide the most effective treatment plan possible.

Although the challenges are great as we strive to treat more children across the country and internationally, provide complex care and expand our clinical and research programs, we're ready. It's a task we accept with pride.

We understand that a HI diagnosis can be a tremendous burden for a family. With that in mind, we offer many resources and amenities to make life easier for families treated at Cook Children's Medical Center. We have a state-of-the-art, all-single room, Level 4 Neonatal Intensive Care Unit (NICU) so families can stay with their baby 24 hours a day, 7 days a week.

We're excited to share information about our program, outcomes and patient resources with you. Feel free to call me directly at any time to discuss a current or potential hypoglycemia case. Thank you for your interest in Cook Children's Hyperinsulinism Center.

Paul Thornton, M.D.
Medical Director
Cook Children's Endocrine and Diabetes Program
Cook Children's Hyperinsulinism Center

About our program

Cook Children's Hyperinsulinism Center is the only one of its kind in the Southern U.S., and the second in the country. The center is led by Medical Director Paul Thornton, M.D., one of the nation's few physicians with extensive clinical and research experience in congenital hyperinsulinism (HI). Actively involved at the international level, Dr. Thornton leads a multidisciplinary team of renowned physicians, researchers and specialists that continue to improve the care and treatment of children with HI. As a result, our program ensures that infants, children and teens with this rare disease receive the most advanced treatments available today.

We have dedicated areas for Endocrinology inpatients—including those in our NICU—with nurses specializing in endocrine and hyperinsulinism diagnoses.

Extending our reach internationally

Sometimes finding the best care means traveling outside of one's country. Since 1989, Cook Children's has served hundreds of international patients. From flight scheduling to accommodations to recreation, our dedicated, multilingual team of providers helps with all the details so families can focus on their child. Our international specialties include Neurosciences, Cardiology, Craniofacial and Cleft Surgery, Endocrinology and Hematology and Oncology. We are expanding our programs, services and amenities to meet the growing needs of families across the globe.

Dr. Thornton played a lead role in the Pediatric Endocrine Society's development of guidelines for the management of hypoglycemia in neonates, infants and children. To learn more, visit pedsendo.org.

Services and collaborative partnerships

Our services

- Endocrinology
- Gastroenterology
- Neonatology
- Neurology
- Pathology
- Pediatric Surgery
- Radiology

Our team of board certified physicians and advanced practice providers

- Paul Thornton, M.D., pediatric endocrinologist, medical director
- Lisa Truong, CPNP, advanced practice hyperinsulinism nurse, co-director
- Susan Hsieh, M.D., assistant director
- Alejandro De La Torre, M.D., assistant director
- Leah Elizondo, M.D., neonatologist
- John Uffman, M.D., pediatric surgeon
- Irene Sanchez, M.D., pathologist
- Barry Putegnat, M.D., radiologist
- Shelby Fierke, M.D., radiologist
- Fernando Acosta, M.D., neurologist
- Jane Keng, M.D., gastroenterologist
- Kaitlyn Miller, RN, coordinator
- Tiffany Skrodzki, RN, research nurse
- Deborah Rafferty, research coordinator
- Minali Patel, endocrine pharmacist
- Jamie Haswell, investigational pharmacist
- Micha Koentz, investigational pharmacist supervisor
- Ryan Murphy, clinical therapist
- Corrie Andrews, clinical therapist
- Teresa Bartnicki, clinical therapist
- Caroline Atwell, registered dietitian
- Ana Neblett, registered dietitian
- Hannah Kim, registered dietitian
- Brenda Sonnier, child life specialist
- Cris Hinojosa, social worker
- Neely, Sit…Stay…PLAY dog therapy

Support system

- Endocrine nurses
- NICU nurses
- Nutritionists
- Social worker
- Psychologist
- Child life specialist
- Feeding and speech therapists

Overview of congenital hyperinsulinism

Congenital hyperinsulinism (HI) is a rare but severe disorder that is the most common cause of persistent hypoglycemia in newborns and children. The estimated incidence of HI is one in 30-50,000 live births, resulting in between 80 to 120 new HI patients each year. Infants with uncontrolled hypoglycemia caused by HI are at risk for seizures or permanent brain damage. Therefore, screening, early identification and aggressive prevention of ongoing hypoglycemia are key factors in preventing irreversible damage and improving quality of life.

There are many types of congenital hyperinsulinism (HI), each treated differently and with different outcomes.

Types of congenital hyperinsulinism

There are many genetic forms of HI with more being discovered each year. Typically, 60% of patients with genetic forms will present in the first week of life with hypoglycemia. These patients will have hypoglycemia that requires a combination of feeding frequently and/or glucose infusion to keep the blood glucose above 70mg/dl. Some may respond to diazoxide, but more than 50% will not and will require surgery to cure the hypoglycemia.

Current best practices suggest that pediatric endocrinologists make a diagnosis of the different forms of HI and determine whether the infant has autosomal recessive diffuse hyperinsulinism or non-mendelian genetic focal disease. Genetic testing can identify exact mutations causing hyperinsulinism. Traditional forms of imaging, such as ultrasound, CT and MRI are not capable of diagnosing focal lesions. Special imaging studies, such as investigational new drug (IND) 18F DOPA, combined with a PET-CT scan, can differentiate focal from diffuse. Because these studies use an IND, they're only available under a research protocol like the study at Cook Children's Hyperinsulinism Center.

Early identification and treatment of these genetic forms of HI is critical to preventing the 20-40% incidence of brain damage seen in these children.

Genetic forms of HI typically present as hypoglycemia in the first week of life.

Diffuse K_{ATP} hyperinsulinism

Diffuse hyperinsulinism is a form of ATP sensitive potassium channel congenital hyperinsulinism (Di-KATPHI) caused by autosomal recessive mutations in ABCC8 or KCNJ11. Infants diagnosed with Di-KATPHI have an abnormal pancreas where all beta cells are abnormal and secrete insulin. When medical therapy fails, surgery is usually required to remove up to 98% of the pancreas. Most of these patients will develop diabetes or persistent hypoglycemia and will need to be managed by an endocrinologist long-term.

Focal K_{ATP} hyperinsulinism

Focal hyperinsulinism is another form of ATP sensitive potassium channel congenital hyperinsulinism (FO-KATPHI) that is caused by an unusual genetic abnormality. These infants have an autosomal recessive mutation in ABCC8 or KCNJ11 inherited from the father and a loss of the normal maternal allele. This causes a small part of the pancreas to secrete insulin, causing hypoglycemia. Because a small portion of the pancreas is affected while the rest of the pancreas is normal, diagnosing patients with FO-KATPHI using IND 18F DOPA combined with a PET-CT scan, allows us to identify which part of the pancreas is affected and remove it. As a result, some patients are cured and have a very low risk of diabetes.

Glutamate dehydrogenase hyperinsulinism

Glutamate dehydrogenase hyperinsulinism (GDH-HI) is the second most common type of hyperinsulinism, and may be referred to as protein sensitive hypoglycemia. It is inherited in an autosomal dominant pattern with many patients having a de-nova mutation. With GDH-HI, the pancreas releases an abnormal amount of insulin in response to both fasting and protein ingestion. Children diagnosed with GDH-HI have elevated ammonia levels at all times and low blood sugar levels after eating protein and an overnight fast. Most diagnoses occur in children more than 3 months old when their diet becomes exposed to a higher protein intake. These children usually respond to diazoxide and rarely need surgery.

Glucokinase hyperinsulinism

Glucokinase hyperinsulinism is a less common form of HI. It's caused by activating mutations in the glucokinase gene, the glucose sensor of the beta cells and is also an autosomal dominant disease. With this form of HI, the set point of insulin secretion is altered so that the beta cells continue to secrete insulin as the glucose falls down to as low as 40-50mg/dl. This causes hypoglycemia that at times may be very difficult to treat. Although the condition is present at birth, the diagnosis may not be made until later. These children may respond to diazoxide, but the most severe will require pancreatic surgery.

Transient neonatal hyperinsulinism

Transient neonatal hyperinsulinism (TNHI) is one of the most common forms of hyperinsulinism (HI) with an estimated 1:10,000 babies affected. Typically, hypoglycemia begins within 24 hours of birth and can last from three to 10 days or up to six months. Often this form of HI is found in infants of a diabetic mother, infants suffering from perinatal stress, infants or mothers with perinatal hypertension, and infants born with IUGR or LGA. However, some babies appear to have no risk factors.

The hypoglycemia may be mild, appearing two to four hours after eating, or it may be more severe with hypoglycemia occurring despite intravenous glucose infusion and/or high-calorie feedings every three hours.

Although TNHI is temporary, it can cause brain damage if left untreated. In order for infants with TNHI lasting longer than seven days to be discharged, they will need treatment with diazoxide and proof that the illness is controlled by fasting eight to nine hours. Most of these patients will need regular visits to an endocrinologist specializing in hyperinsulinism for the next six to 12 months. Hypoglycemia will typically resolve itself during that timeframe.

Insulinomas

Insulinomas are insulin-secreting neoplasms that arise from the beta cells. They are very rare in the general population, occurring in approximately 1-4 per million population. Although the majority occur in adults and are solitary and sporadic, 10% occur in the setting of MEN1. Currently, more than 50% of the insulinoma cases we have followed are in children with MEN1. In these cases, careful consideration should be given to the family history and genetic studies. Typically, imaging by spiral CT, MRI and transesophageal ultrasound may detect many insulinomas > 2 cm in diameter, but 50% of those smaller than this size may be occult. At Cook Children's, we perform arterial stimulation with venus sampling (ASVS) in our dedicated pediatric interventional radiology suite, a procedure that to date has allowed us to localize 100% of the tumors. Together, with our experienced surgeons and pathologist, we have cured 100% of insulinoma cases we've seen.

Cook Children's uses an investigational new drug 18F DOPA combined with a PET-CT scan to diagnose focal lesions in children with congenital hyperinsulinism. These children have a great advantage because with the PET-CT scan, the surgeon is guided to the focal lesion and with the aid of the pathologist, removes it and, in most cases, cures the patient.

Other forms of hypoglycemia treated by our team:

Our team also has the experience to treat patients with the more rare genetic and syndromal forms of hypoglycemia, such as:

- **Genetic**
  - SCHAD HI
  - INS receptor HI
  - MCT1 HI
  - HNF4 alpha HI
  - HNF1 alpha HI
  - Hexokinase HI
  - UCP1
- **Syndromal**
  - Beckwith-Wiedemann HI
  - Kabuki syndrome HI
  - Carbohydrate deficient glycoprotein HI

We also diagnose and treat Nissen fundoplication-induced hypoglycemia and hypoglycemia associated with mitochondrial disease. Together with our metabolic colleagues, we provide a full range of services for patients with glycogen storage disease (GSD), fatty acid oxidation disorders and other disorders of gluconeogenesis.

We offer a full diagnostic program for patients whose exact hypoglycemia diagnosis has not yet been identified.

Why refer to Cook Children's?

Cook Children's offers the only multidisciplinary hyperinsulinism center in the South, available to treat all forms of congenital hyperinsulinism (HI) in children and young adults.

HI is a rare and serious disorder that usually presents within 24 hours of birth or during early infancy. Because HI conditions are difficult to diagnose and manage, care by a specialized multidisciplinary team can shorten hospital stays and improve the patient's outcome. Without early and aggressive treatment, the child may experience seizures, blindness, developmental delays and cerebral palsy.

In addition to offering the very latest in treatment approaches, Cook Children's is involved in leading-edge research on HI. We are actively involved with developing new therapeutic modalities for HI. Some of the current studies under approval by our Institutional Review Board include the investigational new drug 18F DOPA combined with a PET-CT scan, long-term neurological outcomes and genotype phenotype correlation.

Since opening our hyperinsulinism center in 2010, we have consulted, evaluated and treated more than 190 children with recurrent hypoglycemia due to hyperinsulinism. We've also created a family support group and education materials to help our families learn more about this devastating disease.

We've treated more than 302 kids diagnosed with hyperinsulinism.

Diagnosing hypoglycemia

We are happy to accept patients at any stage of the diagnosis and treatment process; however, most physicians typically try diazoxide before referring.

Hypoglycemia < 50 mg/dL is confirmed

Treat with oral feeds and/or IV glucose to keep glucose > 70 mg/dL. Wean off IV if possible. If glucose < 50 mg/dL after 48-72 hours of life, determine etiology of hypoglycemia (measure plasma glucose, insulin, lactate, betahydroxybutyrate, growth hormone and cortisol levels and perform glucagon stimulation test).

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Diagnose with hyperinsulinism

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Treat with diazoxide 5-15 mg/kg/day and evaluate after five days.
Monitor for pulmonary hypertension, fluid overload, neutropenia and thrombocytopenia.

Patient responds; ability to fast 9 hrs with glucose > 60 mg/dL

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Send home and request follow-up with local endocrinologist

Patient doesn't respond

↓

Persistent hypoglycemia

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1. Refer to Cook Children's Hyperinsulinism Center for 18F DOPA PET-CT study
2. Send DNA for hyperinsulinism gene screen

Diagnosis: Diffuse hyperinsulinism
Surgery or conservative
Average length of stay: 38 days

Diagnosis: Focal hyperinsulinism
Surgery and potential cure
Average length of stay: 22 days

When should I refer?

Neonatologists and pediatric endocrinologists can refer patients who have hypoglycemia caused by HI and aren't responding to diazoxide to Cook Children's Hyperinsulinism Center for further evaluation, management and support.

To arrange a patient transfer, please contact Cook Children's Teddy Bear Transport at 1-800-KID-HURT. This team will make all the necessary arrangements, including contacting the HI team to let us know when to expect your patient.

I am referring my patient to Cook Children's Hyperinsulinism Center for evaluation. How can I make the referral process easy on my patient?
We can assist with the referral process. Our team is available and can help:

1. Initiate insurance pre-certification.
2. Locate a place for extended family to stay. Parents can stay in our single-room NICU with their child. Concierge services are also available to coordinate travel and lodging.
3. Keep ongoing communication between our endocrinology team and the referring physician during and after evaluation and treatment.

You've referred your patient. What's next?
Throughout the entire treatment process, our team will work closely with the patient family to provide a safe medical program to manage the patient's disease. We provide families with support, counseling, education and answers to all of their questions. Because many of our patients will need a lifetime of care for their hypoglycemia, we provide ongoing training for parents, caregivers (including the local endocrinologist, pediatrician and/or family practitioner) and patients to help manage the disease through the many stages and changes of the child's life. Our goal is to start this process at admission so families feel comfortable and prepared when it's time to go home.

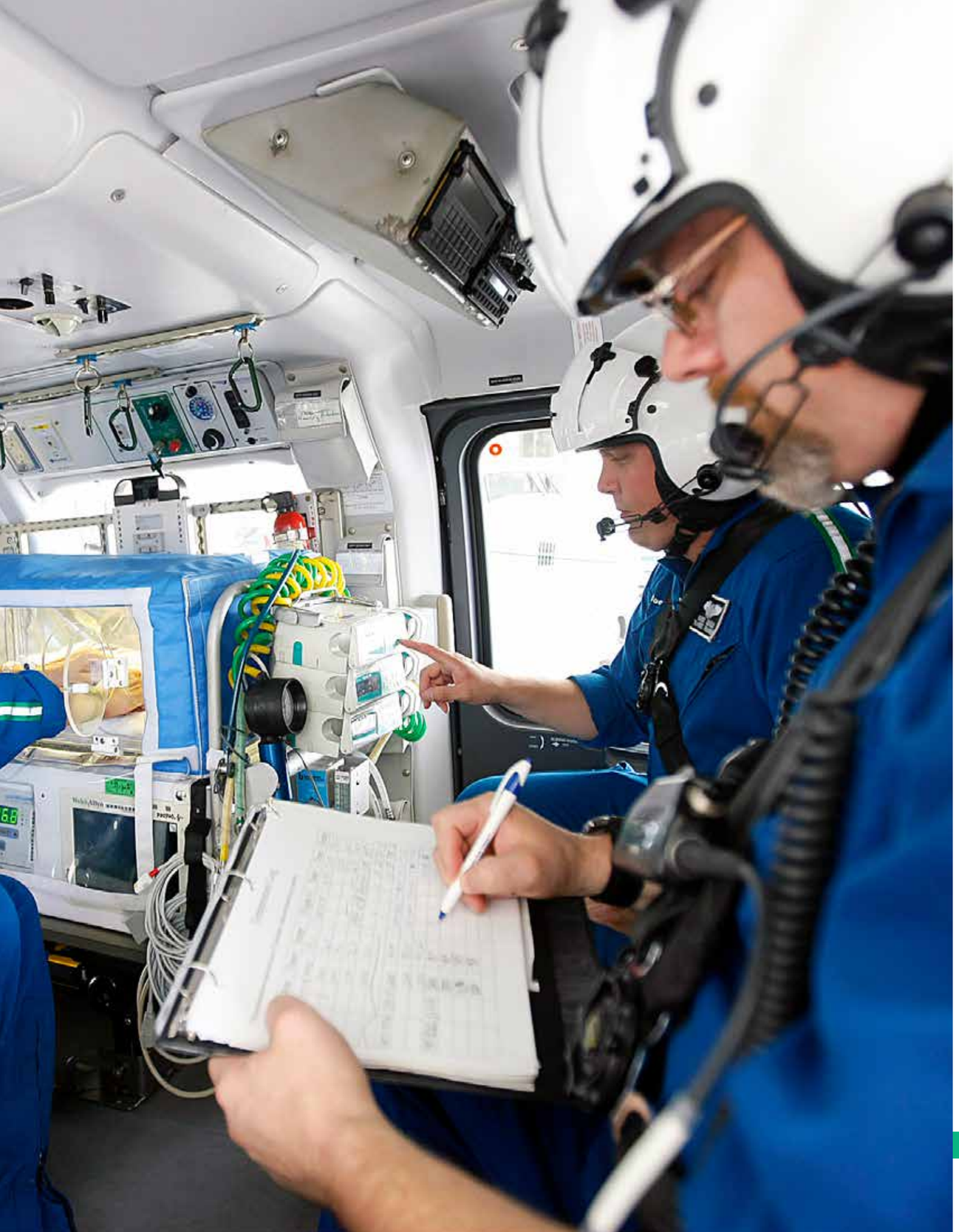
The patient's length of stay will vary, depending on the HI diagnosis. With focal lesions, patients can expect to stay 14 to 28 days, while patients with a diffuse lesion might stay 30 to 50 days. Discharge can occur once a stable and safe program is in place and parents are comfortable with the program. Preparation includes patient education, provision of medication and equipment and a long-term care plan that will involve the local endocrinology team and Cook Children's Hyperinsulinism Center, as needed.

Cook Direct Connect

Cook Direct Connect
682-885-1940 phone
To better serve our treating clinicians, we can assist you with:
- Non-emergent transfer requests
- Direct admissions
- Specialist consultations

Focal patients' average length of stay:
20 days

Diffuse patients' average length of stay:
26 days



Cook Children's Teddy Bear Transport

Babies can be moved safely from the hospital where you delivered to Cook Children's. Our award-winning Teddy Bear Transport Team members are experts in transporting babies who need critical care.

As one of the leading pediatric transport programs in the nation, Cook Children's Teddy Bear Transport:

- Is available to attend high-risk deliveries (1-800-KID-HURT).
- Includes neonatal/pediatric nurses, respiratory therapists and paramedics who are proud to have more than 400 combined years of pediatric transport experience.
- Is one of only a handful of neonatal and pediatric transport teams in the world to receive certification by the Commission on Accreditation of Medical Transport Services.
- Was one of the first teams to use nitric oxide and nitrogen on transports to help babies breathe.
- Can provide hypothermia treatment during transport to help cool a baby's body and allow healing to happen faster.
- Has staff trained in the management of congenital hyperinsulinism.

Our Teddy Bear Transport team brings nearly 4,000 patients to our medical center each year from Canada, across the United States and Latin America.

All-single room Neonatal Intensive Care Unit

Most hyperinsulinism symptoms appear within the first few hours of birth. Our Level IV Neonatal Intensive Care Unit (NICU) offers state-of-the-art technology and a highly experienced staff that cares for babies 24/7.

Newborns admitted with hyperinsulinism receive care in a dedicated section of the NICU. They'll have access to the most current medical technology, a full team of neonatologists and endocrinologists and nurses and specialists who are recognized around the world for their expertise in caring for newborns with hyperinsulinism.

Our NICU single rooms are spacious enough for two adults to stay. Families can take care of their newborn and begin their experience as a family right away. We designed NICU with amenities to help families be as comfortable as possible during their stay.

Single room accommodations include:
- Parent sofa bed with storage
- Rocker recliner to encourage skin-to-skin care
- Breast pump
- Specialized breast milk warmer
- TV with ear buds for parents, so baby can rest undisturbed
- Parent-controlled lighting

Amenities for the families include:
- Parent lounge
- Parent laundry
- Parent showers
- Computer station
- Sibling orientation by a child life specialist
- Complimentary coffee bar
- Weekly family support groups
- Milk bank/storage for mothers
- Mirror, Mirror Hair & Nail Salon and other on-site retail and restaurant options

MAGNET RECOGNIZED
AMERICAN NURSES CREDENTIALING CENTER

Outcomes (December 2023)

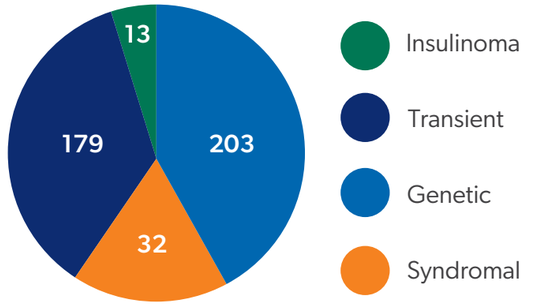
382 Congenital hyperinsulinism patients

99 Pancreatectomies

48 Children with complex ketotic hypoglycemia

93% Surgical cure rate

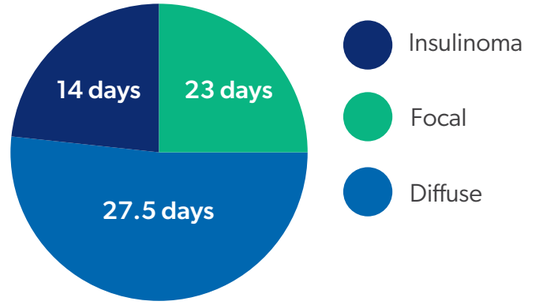
Hyperinsulinism patients



88 PET-CT scans for diagnosis

1 Central line-associated bloodstream infections

Average length of stays for patients



Our Promise

Knowing every child's life is sacred, we promise to improve the well-being of every child in our care and our communities.

Cook Children's
Hyperinsulinism Center
1500 Cooper St., Second Floor
Fort Worth, TX 76104
cookchildrenshyperinsulinism.org

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05.2024