

Patrick J. Javid, M.D.

- A Pilot Study of the Safety and Immunogenicity of the Rotavirus Vaccine in Infants with Intestinal Failure
- Assessment of Hepatic Function in Short Bowel Syndrome Using the Novel 13C-Methionine Breath Test
- Neurodevelopmental Outcomes of Children with Intestinal Failure
- Pediatric Intestinal Failure Consortium



Assistant Professor of Surgery

AWARDS

American Academy of Pediatrics Rosenkrantz Resident Research Award, 2003

John A. Mannick Research Award, Department of Surgery, Brigham and Women's Hospital, 2003

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Pediatric intestinal failure, of which short bowel syndrome is the most common etiology, has been transformed into a chronic disease. Many infants with intestinal failure are surviving to school age and beyond. The evolution of pediatric intestinal failure is directly attributable to advances in medical, nutritional, and surgical treatments of this disease. As such, there are now multiple opportunities for clinically relevant and effective research into different aspects of pediatric intestinal failure.

My research efforts focus on the clinical and translational study of young children with intestinal failure. As a pediatric surgeon with both clinical and academic interests in pediatric intestinal failure, I work with children with intestinal failure on a daily basis and am positioned to study different ways to optimize short- and long-term outcomes. I am an active member of the Intestinal Failure Program at Seattle Children's Hospital, which has both outpatient and inpatient components. Through this program, the pediatric surgeons at our institution work closely with pediatric gastroenterologists and pediatric transplant specialists to tailor the care of each individual child with intestinal failure. The Intestinal Failure Program emphasizes the multidisciplinary aspect of treatment for the child with intestinal failure, and recent data show a distinct mortality benefit from this type of structured care.

The multidisciplinary nature of our clinical program translates nicely into collaborative partnerships for research. I work closely with members of our Divisions of Gastroenterology, Transplantation, and Infectious Disease on multiple research initiatives. In addition, we have full-time support from dedicated pediatric nutritionists, pharmacists, and social workers. My current laboratory includes a surgical resident research fellow, a medical student, and a part-time undergraduate student.

My research investigates a diverse array of issues that pertain to the child with intestinal failure. My current active projects include the following:

A Pilot Study of the Safety and Immunogenicity of the Rotavirus Vaccine in Infants with Intestinal Failure

Infection with rotavirus is the most common etiology of severe diarrhea in the pediatric population. Despite recent attempts at improving prevention, over 600,000 infants worldwide die each year from rotavirus-related gastroenteritis. In the United States alone, rotavirus results in 27,000 hospitalizations, 360,000 emergency room visits, and 374,000 clinic visits each year. In 2006, an oral rotavirus vaccine was approved for use by the Food and Drug Administration, and routine immunization of infants was recommended by the Centers for Disease Control and Prevention and the American Academy of Pediatrics.

Rotavirus is known to cause severe clinical manifestations in infants with intestinal failure, including electrolyte imbalance, dehydration, and prolonged hospitalization. Such patients appear to be more susceptible than healthy children to the infection. Importantly, rotavirus has been shown to delay intestinal adaptation and tolerance of enteral nutrition in children with intestinal failure.

To date, there are no published data as to the utility of rotavirus vaccination in the pediatric intestinal failure population. Given this group's differences in intestinal motility, bowel surface area, and gut-associated immune system, the effect of the vaccine in this population remains unknown. This active pilot study is measuring the safety and immunogenicity of the rotavirus vaccine in pediatric intestinal failure patients. The hypothesis of the study is that a currently approved rotavirus vaccine will be safe and will induce serum immunogenicity to rotavirus in children

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with intestinal failure. The study is designed as a prospective pilot study that will focus on the evaluation of adverse events unique to this population after the administration of the vaccine. In addition, the study will incorporate bench laboratory methodology to measure stool shedding of the virus and systemic absorption of the vaccine, variables which can affect vaccine safety in this cohort. The study will assess seroconversion by measuring immunoglobulin specific to rotavirus.

Ultimately, if the pilot data demonstrate that the rotavirus vaccine is safe in this cohort, the study will serve as the foundation for a multi-center prospective study throughout the Pediatric Intestinal Failure Consortium (PIFCon).

Assessment of Hepatic Function in Short Bowel Syndrome Using the Novel ¹³C-Methionine Breath Test

Infants with short bowel syndrome are at risk for liver disease associated with the use of parenteral nutrition (PN-associated liver disease, or PNALD). This carries a high mortality rate. Indeed, the long-term survival of children with short bowel syndrome is limited primarily by the progression of liver disease. Current tests used to evaluate PNALD, such as hepatic transaminases and bilirubin, may not accurately assess hepatic function, and the prothrombin time is generally not elevated until late in the course of liver injury. Moreover, histopathology evaluation is not routinely available given the morbidity associated with liver biopsy. It has also been demonstrated that prolonged administration of PN can impair the function of hepatic mitochondria, similar to the liver injury induced by hepatic cirrhosis and fatty liver. These data suggest that assessment of hepatic mitochondrial function may be an appropriate marker for liver injury in patients dependent upon PN. This study proposes to validate an innovative measure of mitochondrial liver function in children with short bowel syndrome.

Non-radioactive, stable isotopes have been used safely and effectively for decades to obtain functional assessments of several organ systems. The present study proposes to use a stable (i.e., non-radioactive) isotope breath test to

measure synthetic liver function in conjunction with the liver biochemical profile (bilirubin, transaminases and prothrombin time). The test involves administering a substrate that is metabolized primarily by the liver (the stable isotope L-[1-¹³C]-methionine) and collecting byproducts of liver metabolism in expired breath (¹³CO₂). We hypothesize that the ¹³C-methionine breath test (¹³C-MBT) will provide a quantitative measure of synthetic hepatic function that can be used in conjunction with current biochemical liver tests to better evaluate the degree and progression of PNALD in patients with short bowel syndrome.

Methionine is an essential amino acid metabolized by the liver through the primary pathway of transmethylolation. The transmethylolation of methionine by adenosyltransferase into homocysteine occurs only in the liver, as other tissues lack the required enzymes. S-adenosyl-L-methionine is converted into S-adenosyl-homocysteine by the hepatic enzyme N-methyltransferase. This enzyme functions to remove methyl groups, leading to excretable byproducts; the major pathway to remove excess methionine methyl groups is via sarcosine production. Sarcosine is oxidized by sarcosine dehydrogenase to produce a one-carbon fragment that can be subsequently converted to CO₂. Sarcosine dehydrogenase is oxidized by the mitochondrial oxidation system, and the sarcosine oxidase system is present exclusively in hepatic mitochondria. Therefore, measuring the labeled CO₂ byproduct of ¹³C-labelled methionine in samples of expired breath represents a unique and promising technique to evaluate the oxidative capacity of liver mitochondria.

This study is active and funded by the Seattle Children's Hospital Academic Enrichment Fund. We are performing this study in close collaboration with pediatric surgical investigators at Children's Hospital Boston, where this study was first trialed. Our ultimate goal is to combine our data into a multi-institutional, federally-funded study to study this innovative technique in a broad cohort of children with intestinal failure.

Neurodevelopmental Outcomes of Children with Intestinal Failure

Children with intestinal failure are at high risk for poor neurologic and cognitive development. These patients often undergo multiple complex operations under general anesthesia, which has previously been shown to be a risk factor for impaired cognitive development. Indeed, recent data have shown that premature neonates who require surgery for necrotizing enterocolitis (NEC) have worse neurodevelopmental outcomes than neonates with non-operative NEC. Children with intestinal failure require multiple prolonged hospital stays, another factor demonstrated to negatively affect cognitive development in children. In addition, dependence on parenteral nutrition, which is common in these patients, can lead to a high incidence of indwelling central venous lines and subsequent blood stream infections that can predispose to sepsis. Systemic infections have been correlated with neurodevelopmental impairment in several cohorts of children. Finally, these children are often hemodynamically unstable during the neonatal period due to their primary diagnosis, thereby increasing the risk of neurologic injury early in life.

Despite these risk factors for impaired cognition, there is scant data in the literature focusing on the neurodevelopmental outcomes of these patients. Given their risk factors for neurodevelopmental impairment and the fact that these children can expect to reach school age and beyond, effective study of neurodevelopmental outcomes in this population would contribute valuable data that may impact their clinical care. This research will allow for the identification of patients at high risk for poor neurocognitive development, and may lead to the implementation of early intervention programs to improve development and quality of life.

This pilot study aims to measure the neurodevelopmental status of young children with intestinal failure using validated tools and to compare these to well-accepted normative values. The hypothesis of this study is that children diagnosed with intestinal failure will have substandard neurodevelopmental outcomes due to their unique and multiple co-morbidities when compared with well-accepted normative values. The study focuses on children aged 1 to 3 years, as this serves as an ideal time to implement early intervention programs in

those children at highest risk for cognitive impairment. A secondary aim of this study is to identify potential predictive risk factors for neurodevelopmental impairment in this group.

This study has been designed to maximize the resources available at Seattle Children's Hospital (SCH) and the University of Washington Medical Center (UWMC). All patients will be recruited from the active census at the SCH Intestinal Failure Program. Subjects will undergo a focused neurodevelopmental evaluation at the University of Washington High-Risk Infant Follow-Up Program (HRIF), which has specialized in the measurement of neurologic impairment of premature infants and children for over 30 years. Neurodevelopmental indices in this cohort will be evaluated through validated and well-established tools that have been utilized for decades to assess the neurodevelopmental status of numerous cohorts of young children. These tests will include a focused physical examination to document hearing and visual impairment, and cerebral palsy, as well as a neurocognitive evaluation using the Bayley Scales of Development or Stanford-Binet Intelligence Scales. These neurocognitive tests incorporate well-defined control data that will allow comparative analysis of our chosen study cohort with healthy, aged-matched children.

This study has the potential to serve as a preliminary benchmark for the neurological, cognitive, and developmental status of long-term survivors of pediatric intestinal failure. As survival continues to increase in children with this disease, the information gained from the study may be invaluable in the future care of these patients. For example, early identification of children in this cohort at risk for long-term neurodevelopmental impairment may allow for the implementation of early intervention services to improve overall outcome. In addition, the study has been constructed to allow for future long-term follow-up in a well-established facility with a consistent team of experienced investigators. Finally, the pilot data obtained from this study may serve as a foundation for a future multi-institutional study within the existing Pediatric Intestinal Failure Consortium (PIFCon), thereby increasing the size of the subject cohort and the power of the study.

It is anticipated that this study will start enrolling subjects in late 2010.

Pediatric Intestinal Failure Consortium

The Pediatric Intestinal Failure Consortium (PIFCon) is a multidisciplinary collaborative network constructed to effectively study the management of pediatric patients with intestinal failure. Its research efforts include basic science as well as clinical and translational techniques. The collaborative is composed of pediatric practitioners from 18 academic centers throughout the US and Canada; in fact, SCH was an original member of the consortium. The group has active funding through the NIH (1R21DK081059-01), and PIFCon is currently applying for additional grant support through the NIH U01 mechanism.

Seattle Children's Hospital was a founding member of PIFCon, and members of the Intestinal Failure Program play an active role in its leadership. PIFCon has collected retrospective data on children with intestinal failure from all 18 centers, and additional federal funding will allow for the collection of prospective data. This data will be available to analyze with the support of PIFCon statisticians. Our laboratory will take an active role in acquiring and analyzing this data to help define the clinical parameters and treatments that optimize long-term outcomes in children with intestinal failure.

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