Digestive Diseases Interagency Coordinating Committee (DDICC)

Short Gut and Small Bowel Transplantation
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National Institutes of Health
Building 31, Room 9A22
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Participants

Chair:

Jay H. Hoofnagle, MD	Director, National Institute of Diabetes and Digestive and Kidney Diseases

Executive Secretary:

Stephen P. James, MD	Deputy Director, National Institute of Diabetes and Digestive and Kidney Diseases

Members:

Brian E. Harvey, MD, PhD	Senior Medical Officer, Food and Drug Administration, Office of Device Evaluation, Center for Devices and Radiological Health
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Patricia Robuck, PhD, MPH	Director, Clinical Trials Program, National Institute of Diabetes and Digestive and Kidney Diseases
Allen Spiegel, MD	Director, National Institute of Diabetes and Digestive and Kidney Diseases

Speakers:

Mitchell B. Cohen, MD	Professor of Pediatrics, Cincinnati Children's Hospital Medical Center, President NASPGHAN

Thomas M. Fishbein, MD	Chief, Intestinal Transplantation, Recanti/Miller Transplantation Institute, the Mount Sinai School of Medicine
Stuart S. Kaufman, MD	Chief, pediatric Intestinal Transplantation Medicine, The Mount Sinai School of Medicine
Thomas Ziegler, MD	Associate Professor of Medicine, Emory University School of Medicine, Divisions of Digestive Diseases and Endocrinology

Guests:

Darla Danford, MPH, DSc	Nutrition Coordinator, National Heart, Lung, and Blood Institute
Philip Sherman, MD	Co-Chair, NASPGHAN/CDHNF Research Agenda Committee, Hospital for Sick Children
Lisa Gansheroff	National Institute of Diabetes and Digestive and Kidney Diseases

Welcome

Jay H. Hoofnagle, M.D., Director of the Division of Digestive Diseases and Nutrition at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and Chair of the Digestive Diseases Interagency Coordinating Committee (DDICC), welcomed the participants to the meeting on Short Gut Syndrome (SGS).

Clinical and Mechanistic Aspects of Short Gut Syndrome

Dr. Thomas Ziegler, Associate Professor of Medicine at Emory University, School of Medicine, Division of Digestive Diseases and Endocrinology, defined Short Gut Syndrome (SGS), as a consequence, together with malabsorption, of an underlying disease that results in the need for surgical resection or surgical bypass. Clinical consequences are extremely individual, and include diarrhea, steatorrhoea, dehydration, malnutrition, weight loss, and manifestations of vitamin and mineral deficiencies, all of which are especially devastating for patients who require nutritional support.
The mechanisms of malabsorption are relatively straightforward, in that the patient has a shortened bowel due to surgical removal and that the residual bowel is often diseased. Patients exhibit acid hypertension, rapid intestinal transit, loss of surface area, impairment of the residual mucosa, bacterial overgrowth, and bile wasting and the consequences thereof.

Clinical severity of SGS is determined, at least in part, by the extent and site of resection, as well as by residual disease. Individuals who have undergone resection of the ileum and colon experience a relative deficiency of endogenous growth factors, such as peptide-2. There is also evidence that loss of ileosecal valve contributes to bowel overgrowth.

Clinical etiologies of SGS among adult patients encompass a large range, including:

- Crohn's Disease;
- patients with atherosclerosis and a thrombosis of the severe and mesenteric artery and subsequent mesenteric infarct;
- volvulus or malrotation, causing ischemia of the bowel;
- multiple bowel resections with post-surgical complications or trauma; and
- radiation injury (among women).

Dr. Ziegler indicated that SGS is clearly an orphan disease. Approximately 20,000 patients in the United States have chronic parenteral nutrition-dependent SGS, and a group in Canada estimates pediatric short gut incidence at 4.8 million patients per year, with no evident gender or ethnic predisposition. Data from recent studies suggests that the increased incidence may be due to improved surgical techniques and post-operative care, and increased experience with TPN. Still, a better estimate of afflicted patients is needed, as is data on the morbidity and mortality of P-non-independent SGS patients. The decreasing use of malabsorptive bariatric surgery also presents an interesting avenue for research.

Although hyperplasia or adaptive growth response in animal models is not reflected in human clinical studies, there is some evidence that an increase in nutrient and fluid absorption does occur over time. This apparent improvement in both growth and function may be due to increased expression or function of mucosal growth factors and growth-related peptides, as evidenced by a number of animal studies showing that levels of IgF1 (interglucon), together with other growth factors present in the mucosa, increased following resection. Additional potential adaptive mechanisms include increased residual bowel exposure to pancreatic biliary sections containing growth factors and glutathione, and exposure to malabsorbed carbohydrate, which may play a role in terms of fluid, energy, and sodium absorption due to short-chain fatty acid production by fiber and carbohydrate fermentation. Current investigations are also focused on the role of gut mucosal redox status.

Dr. Ziegler emphasized that a key issue in current research is whether or not gut mucosal growth occurs in humans in the same manner in which it does in animal models. Data from human studies is admittedly limited and warrants further attention, especially in terms of time course, post-surgical benefits, and site-specific bowel growth.

Similarly, there is a paucity of clinical data regarding nutrient absorption. Dr. Ziegler presented data from one study that examined the pepti-one transporter, a major mediator of transporter di- and tri-peptides from the intestinal lumen into the intrasite, where peptides are broken down into free amino acids and small amounts of peptides are transported directly into portal blood. Data revealed several significant results. Perhaps most important was the finding that patients with SGS experienced a five- to eight-fold increase in up-regulation of pepti-one only in the colon, despite no change in colonic crip depth compared to control patients, representing the first data of a nutrient transporter being up-regulated in humans, and suggesting that the colon has the capacity to potentially adapt to the post-resection situation by increasing its ability to transport di- and tri-peptides. However, Dr. Ziegler cautioned that this might prove to be a double-edged sword, in that pepti-one has been shown to also transport FMLP, which could have a pro-inflammatory chemotactic-type effect.

Animal studies have provided evidence that with parenteral feeding, the small bowel and colon undergo an atrophic response, accompanied by decreased gut barrier function, both at the anatomic and immune level, and decreased absorptive function in the form of down-regulation of digestive enzymes and nutrient transporters. A lack of parenteral feeding results in decreased pancreatic and biliary secretion, cholestasis, altered gut flora, and decreased gut mucosal levels of gutrophic peptides. Although these animal studies have provided important data, a greater and more complete understanding requires more research with human subjects.

Clinical management of patients with SGS is highly individualized, since care is based on dietary tolerance, residual bowel anatomy, and residual bowel function, all of which vary significantly among subjects. Still, some generalizations can be made with regard to aspects of care. Oral rehydration fluids, small frequent feedings, and a low fat/high protein diet are primarily emphasized. Oral rehydration fluid is an especially important factor of dietary care for patients with SGS, and an area, which needs to be examined more closely.

Approximately 50,000 patients in the U.S. require home TPN, a significant number of whom have SGS. Parenteral nutrition is not only costly (care runs approximately $100,000 per year), but also involves medical complications and quality of life issues that warrant further research attention.

Mortality rates for patients with SGS are about 25 percent in a 3- to 5-year period among individuals who do not have malignancy. Messing's study provided data showing that out of 124 adults without malignancy who had TPN-dependent SGS, 2- and 5-year survival rates were 86 percent and 75 percent, respectively, and that approximately 50 percent of those patients required TPN at 2 and 5 years, respectively. Study results indicated the importance of the ileum and the residual colon in terms of improving outcomes. Therefore, methods to enhance the function of the residual ileum or the residual colon, regardless of size, would be a very active area of important research.
Research is currently being conducted on methods to enhance gut adaptation via increasing surface area and improving nutrient transport capacity. Areas of study include enteral feeding, use of specific nutrient substrates, growth factors, and combined dietary-growth factor therapy. Standard intravenous nutrition does not provide at least some of the known gut-tropic substrates (e.g., short-chain fatty acids, glutamine, fiber, small peptides, or glutathione).

Dr. Ziegler emphasized the importance of further research in the area of growth hormones. It has been suggested that when receptors are present throughout the human small and large bowel, growth hormone treatment induces tissue IgF1, which has been shown in animal studies to have gut-tropic effects. Several experimental models of colitis have demonstrated enhanced colonic and anastomotic strength, along with mucosal growth and repair, following the use of growth hormone treatments. Water, electrolyte, and L-amino acid transport have been similarly enhanced in experimental animals treated with growth hormones. It is widely accepted that growth factors have whole body anabolic effects, enhance the utilization of nutrients for cellular growth and repair, and that nutritional status conversely is very important for growth factor production and action.

Given the small number of SGS patients and their heterogeneity, Dr. Ziegler suggested that consortium-type approaches might be the most cost-effective means for government-funded research, in terms of better defining etiology, morbidity, mortality, and to facilitate larger sample

sizes and standardization of therapy in trials of SGS. Detailed assessment of the small bowel and colonic mucosal growth response in expression and function of nutrient transporters at different times of bowel resection, as well as more information on gut mucosal changes at the growth and functional level, nutritional status, and morbidity associated with non-TPN-dependent forms of SGS, are areas that need to be explored.

Dr. Ziegler also suggested that additional research be conducted in:

- oral rehydration solutions and their potential applicability to a wide variety of patients;
- dietary patterns, specific foods, and nutrient supplements
- novel delivery systems;
- regulation and endogenous adaptive changes in terms of proliferation, apoptosis, regulators, nutrient transport expression and regulation;
- mechanisms and interactions of combinations of nutrients and growth factors in the in vitro and in vivo settings to identify more mechanistic patterns; and
- the use of genomics, proteinomics, and metabolomic approaches.

In response to a question regarding the burden on Medicare, Dr. Ziegler replied that the Medicare data published in 1995 in *Gastroenterology* needs to be revisited.

Medical and Surgical Aspects of Small Bowel Transplantation

Dr. Thomas M. Fishbein, Chief of Intestinal Transplantation, and Dr. Stuart S. Kaufman, Chief of Pediatric Intestinal Transplantation Medicine at The Mount Sinai School of Medicine, presented the medical and surgical aspects of small bowel transplantation.

On October 4, 2000, CMS approved intestinal transplantation, with the following primary criteria: 1) patients must fail parenteral nutrition, 2) centers must perform more than 10 transplants per year, and 3) patient survival rates must exceed 65 percent in one year. Currently, only four centers in the United States meet this criteria (Mount Sinai, Pittsburgh, Miami, and Nebraska), although the number of initial bowel transplants has increased over time, from fewer than 10 in 1985 to over 100 in 2001.

Indications for bowel transplant include recurrent line sepsis, fungal line sepsis, or single episode sepsis with HD instability; non-reconstructible GI tract; liver cholestasis (i.e., impending liver failure); loss of access (two major vessel thromboses); and recurrent dehydration. Over 60 percent of adult patients who undergo a bowel transplantation will have SGS.

Over the past 5 years at Mount Sinai, 60 percent of patients were listed for intestinal transplants, 13 percent required bowel rehabilitation, 14 percent were assigned indefinite parenteral nutrition, and 15 percent could remain on TPN life-long.

Dr. Fishbein discussed the outcome of intestinal failure without transplant in patients who have a life-long TPN need, and pointed out that the outcomes differ between adult and pediatric patient populations. For adults, 25 percent will remain on TPN indefinitely. The majority of patients will actually rehabilitate and come off of TPN. However, over 5 years, somewhere between 25 and 40 percent of adult patients will die on TPN. Unlike their adult counterparts, only 10 percent

of pediatric patients will end parenteral nutrition (PN), usually after 1 to 2 years. Ten percent will remain on PN indefinitely, and 10 percent will die on PN.

Dr. Kaufman outlined the predictors of permanent parenteral nutrition in adults. Adult patients with small intestines of less than 100 cm with ar-enterostomy, those with small intestines less than 50 to 65 cm with some colon and no ICV or small intestines less than 35 cm with all colon and ICV, patients suffering from an underlying mucosal disease (IBD/radiation), and those with motility disorders, have indicators for permanent parenteral nutrition. (p 23-24)

Preliminary study data shows that bilirubin in post-transplant patients slowly returns to normal levels, suggesting that cholestatic liver disease may be resolved by 6 months post-transplant. Fibrosis may also regress following transplantation.

Current transplant protocols are divided between immunosuppression (e.g., tacrolimus, sirolimus, basilizimab, steroids, and II TX (-) cytotoxic x-match pretransplant (T-cell)) and prophylaxis (e.g., ganciclovir IV x 2 wk, then follow CMV PCR, Cytogam, 12 wk, no CMV matching for multi-organ recipients, CMV (-) blood, and standard antibiotics).

Small intestine (less than 30 to 40 cm), absence of ileocecal valve, some colon resection, and minimal tolerance of enteral feeding within 2 to 3 months after resection, are predictors of permanent TPN in infants with Short Gut.

Liver disease in patients with SGS is similar to normal gut patients, in terms of high intra-hepatic resistance levels. However, SGS patients differ from normal gut patients in that they experience low mesenteric blood flow, less porto-systemic shunting, and more passive bowel congestion.

Drs. Fishbein and Kaufman outlined the probable early predictors of parenteral nutrition-associated failure, (hyperbilirubinemia greater than 3 to 4 mg/dL beyond age 3 to 6 months, and portal hypertension (splenomegaly, dilated superficial abdominal veins, and thrombocytopenia)), and discussed the prognostic value of liver biopsy, severity of portal HTN, elevated AST, ALT, GGT, and the absence of esophagogastric varices and ascites.

Common early problems in postoperative management of small bowel transplantation include frequent abdominal sepsis, gastroparesis, and prolonged mechanical ventilation, especially in liver/intestinal transplants and infants. Drs. Fishbein and Kaufman explained the dietary goals for postoperative recipient management, and emphasized that a key issue for postoperative management involves frequent graft rejection. The historically high incidence of early graft loss warrants early diagnosis requiring surveillance endoscopy, which is both invasive and has limited sensitivity and specificity. The current standard diagnosis of rejection is based on endoscopic biopsy, concurrent liver rejection, and an inconclusive histology. Drs. Fishbein and Kaufman suggested alternative diagnoses using viral enteropathy and dietary intolerance or hypersensitivity.

Complications from rejection under old immunosuppressive therapies include frequent exfoliative rejection, recurrent high-dose corticostroids and anti-T cell antibodies, and fatal sepsis. Morbidity associated with these therapies includes CMV and EBV infections. In contrast, morbidity associated with new immunosuppression is characterized by reduced early mortality (yet continued dysfunction) and emergence of new viral enteropathies, such as

adenovirus, caliciviruses, astrovirus, coronavirus, and orbivirus. Further, Drs. Fishbein and Kaufman pointed out in the case of these "new" graft pathogens; children appear more vulnerable than adults. Non-invasive tests are generally either unavailable or insensitive. Endoscopic results are typically non-specific and insensitive, with nondiagnostic histopathology that mimics rejection. There is a lack of any effective therapy and potential precipitation of rejection.

Viral cultures at Mount Sinai showed significant pediatric adenovirus infections. Calicivirus was characterized by transient diarrhea linked to food or nosocomial sources in both children and adults. Though not traditionally recognized in intestinal transplantation, Mount Sinai had four pediatric cases of calicivirus infection by nucleotide sequencing. Typical features of post-transplant caliciviral enteritis include 100-mg/kg/d secretory diarrhea for 50 to 100 days, TPN, and reduced immunosuppressive therapy, which promotes secondary rejection. Drs. Fishbein and Kaufman presented information regarding improved adult and pediatric survival rates and benefits of "new immunosuppression" therapies on graft survival.

Drs. Fishbein and Kaufman offered the following summary points:

- Liver disease is more common than previously recognized, both in children and adults.
- High pre-transplant mortality exists for individuals with SBS.
- Rejection remains the primary obstacle (not GVH or reperfusion injury).
- Rejection and viral infection are difficult to discern, and both are common occurrences.
- Children and adults have similar survival, but children have more morbidity.
- Isolated intestinal transplants yield higher survival than multi-organ recipients (except rats).
- New agents are improving outcomes, but no clear explanations exist.
- There is no vested interest of industry to support research.

One of the key problems in intestinal translation is patient death while listed for transplantation. If liver disease is progressive, it is in the patient's best interests to do an isolated intestinal transplant before the damage becomes irreversible. Doing so requires a better understanding of the causes of PN-associated liver disease, better predictability of liver disease progress, and therapies to stave off liver disease in infants. To that end, Drs. Fishbein and Kaufman proposed funding the following: A national clinical TPN/intestinal failure database, including lab, clinical/demography, and histology; studies that identify non-invasive early markers of liver disease; studies that identify molecular basis of cholestasis in TPN disease; and therapies to slow the natural history of liver disease, particularly in children.

A second issue that needs to be addressed with regard to intestinal transplantation is the prevalence and severity of rejection. Rejection in this area of transplantation is more common and worse than with other organs. New agents have improved this, but still no good understanding of their mechanisms exists. Rejection is similar to IBD, but minimal research is

currently underway that takes advantage of advances in mucosal immunology. Again, Drs. Fishbein and Kaufman suggested areas that ought to be funded in this area. To bridge the gap between IBD and SB transplants, studies need to be conducted which examine mucosal regulatory function, differences between gut lymphocytes, and methods for achieving specific immunosuppression. Simultaneously, researchers ought to de-emphasize old issues, such as GVH, hepatic protection, and chimerism. Studies should explore tolerance induction in the bowel, seek an understanding of apoptosis (as enterocytes, lymphocytes, or another), focus on human tissue or serum, and target newer immunosuppression in the allograft.

Morbid and labor intensive care presents another concern for small bowel transplant patients. Patients require stoma for frequent endoscopy to diagnose rejection and other pathologies. Patients (particularly babies) have frequent readmissions for secretory diarrhea, and require frequent early reoperations. The identification of minimally or non-invasive markers for injury, allowing only directed endoscopy and biopsy (no stoma), is therefore an area for research. New agents need to be sought to control secretory diarrhea, and clinical trials of antidiarrheals should be conducted.

Finally, infectious diarrhea is more common, more severe, and lasts longer in intestinal transplant patients than in other transplant recipients. These individuals abnormal response to infection presents a unique opportunity to study oral tolerance. Clinical investigations in the area of cryptogenic secretory diarrhea after transplant, with a focus on viral mediation, antidiarrheals, and oral tolerances, were recommended.

Research opportunities in short gut syndrome

Dr. Mitchell B. Cohen, Professor of Pediatrics at Children's Hospital Center and President of NASPGHAN, continued the discussion of research opportunities in intestinal failure, stating that since 10 to 15 percent of patients with intestinal failure will require intestinal transplantation, determining which patients will need it and when is an important research goal.

The decreased incidence of what Dr. Cohen referred to as "intractable diarrhea" is due to a number of factors, including more appropriate feeding techniques, significant advances in parenteral nutrition, availability of elemental formulae to assist patients through a transient period, and a decrease in incidence of infectious agents. Elimination of this "bottom of the iceberg", as Dr. Cohen termed it, together with improved neonatal/surgical care and better enteral/parenteral feeding techniques has caused an increased survival rate for patients with intestinal failure.

To facilitate discussion and focus research efforts, Dr. Cohen proposed both a general definition of intestinal failure (reduction in functional gut surface area below the minimum amount necessary for absorption of nutrients) and an operational definition (the requirement of more than three-fourths of total calories delivered by parenteral nutrition for at least 1 month).

Causes of intestinal failure include:

- Short Bowel Syndrome (SBS), of which volvulus and necrotizing enterocolitis are the most common in pediatrics;
- structural enterocyte disorders, such as microvillus inclusion disease or tufting

enteropathy;
- motility disorders, such as Hirschprung's Disease and pseudo-obstruction;
- autoimmune enteropathy;
- food intolerance or allergic disorders; and
- congenital transport defects.

Compiled data from the Italian Society of Pediatric Gastroenterology's clinical network indicates that SGS accounts for nearly 45 percent of intestinal failure, followed by nearly equal amounts of structural enterocyte disorders and motility disorders, food intolerance, and autoimmune enteropathy.

With approximately 20,000 patients in the U.S. having an annual cost of $150,000 per year in TPN requirements alone, the economic impact of SGS is significant. A 10 percent decrease in the need for TPN would result in a $300 million savings, excluding other costs, such as small bowel transplantation hospitalizations.

The complexity of intestinal failure gives rise to a number of research opportunities. Dr. Cohen proposed nine general areas for goals in intestinal failure research, and provided examples from current study subjects for each of these categories:

- To prevent SGS, including necrotizing enterocolitis
- To classify other causes of intestinal failure, i.e., recognition of new syndromes and diseases
- To define natural history of these diseases
- To optimize resources, sharing and developing current and new expertise
- To identify basic and translational research opportunities to increase intestinal adaptation
- To prevent the complication of therapy
- To improve the quality of life
- To optimize transplantation for those patients who require it
- To identify alternatives to transplantation.

Dr. Cohen emphasized the need for clear disease definition, since subtypes of autoimmune enteropathy, structural enterocyte disorders, and motility disorders may be a continuum of different diseases. Without adequate definitions, the molecular causes and appropriate treatment strategies are much less likely to be found.

Proper classification of diseases is necessary in order to understand their natural history. In addition, the effect of environment and modifier genes must be studied. The combined effects of primary epithelial, immunologic, and motility disturbances in this population need to be defined, and a clinical approach towards intestinal failure needs to be standardized. Optimizing resources will aid in reducing the number of misdiagnosed cases.

Basic and translational research opportunities include the evaluation of feeding regimens to maximize digestion, absorption, and adaptation; examination of the role of intestinal transporters, inflammatory mediators, transcription factors, cell adhesion molecules, gut flora, and growth factors in modulating intestinal failure; understanding the effects of up-regulating peptide transporters; and definition of the role of other transporters.

The role of adhesion molecules in promoting gut integrity and morphogenesis, as well as other factors, which regulate mucosal integrity, the host bacteria relationship (the exploitation of gut flora to help decrease inflammation or promote absorption). Translational studies involving growth factors that can promote adaptation, including growth hormone are currently underway, but cannot be done in single centers.

In intestinal failure, translocation from the gut is the source of sepsis, and little is known about the immune defects in intestinal failure. More information is needed on the role of dysmotility, as well as microbial ecology.

TPN-associated liver disease is of particular concern for pediatric patients. Research needs to be conducted to identify effects of physical separate from nutritional dependence on TPN, and to examine the effects of body image distortion, as well as the social and educational outcomes related to interventions and the timing of interventions, with regard to quality of life outcomes for patients or for parents of children with intestinal failure.

Better graft survival, reduced sepsis (including viral sepsis), and reduced post-transplant liver proliferative disease depend on the determination of optimal timing of transplantation based on disease and natural history, and the development of improved methods of immunosuppression.

Researchers need to develop alternatives to transplantation, including improving and validating surgical procedures to lengthen the bowel, to identify the intestinal stem cells and their function, to deliver pleury potent stem cells from other organs and/or bone marrow, to be able to influence cell lineage and commitment in the intestine, and to develop neomucosis.

Dr. Cohen summarized these priorities for SGS research:

- Integrate the basic and clinical science with good basic science studies and a functional clinical research network.

- Define natural history of these diseases, and determine the role of genotype and environment on phenotype.

- Optimize resources, sharing and developing the expertise in those centers that have expertise into regional or national centers.

- Provide network opportunities for translational research.
- Prevent complications of therapy.

- Address center-to-center variability in practice with outcome or evidence-based data.

- Improve the quality of life and define the quality of life outcomes for patients and parents.

- Optimize transplantation for those who need it.

- Identify alternatives to transplantation.

In response to a comment regarding the advantages of developing a registry as opposed to a network, Dr. Cohen expressed concern that data in a registry need to be validated, and considering the expense of good data input and good data validation, a registry may not be as cost-effective an option as a network.

Adjournment

Dr. Hoofnagle thanked the participants and the DDICC committee members and adjourned the meeting.