MassGeneral Hospital *for* Children™

Cascades

WINTER 2011 NEWSLETTER TO PHYSICIANS

FROM THE CHIEFS

Dear Colleague,

In the rapidly evolving environment in which we care for our patients, MassGeneral *for* Children (MG*f*C) strives to continually meet the needs of community pediatricians with specialized consulting and referral services. This issue of *Cascades* details the resources available to you for the care of infants, children, and young adults with GI diseases. Two new programs introduced here, the Food Allergy Program and the Hepatobiliary and Pancreatic Program, illustrate our multidisciplinary approach to diagnosis and treatment that involves primary care physicians and families. The third article introduces efforts in our translational research lab to improve the lives of our youngest patients, neonates. Necrotizing enterocolitis (NEC) is a disorder that often presents in the neonatal period and causes life long medical challenges, including short bowel syndrome. Our efforts are aimed at characterizing this disease, identifying genetic predictors that will help distinguish which infants need increased monitoring, and providing ongoing collaboration with pediatricians caring for children affected by NEC.

If you have any questions about our specialized programs, we hope you will contact us at 888-644-3211. We appreciate your trust in allowing us to share in the care of your patients, and hope to hear from you if there are ways we can better serve you.

Ronald Kleinman, MD
Physician-in-Chief
MassGeneral Hospital *for* Children

Joseph P. Vacanti, MD
Surgeon-in-Chief
MassGeneral Hospital *for* Childrem

Comprehensive Food Allergy Program Integrates Research, Education

For reasons that are currently unknown, the incidence of food allergies is increasing, affecting up to eight percent of children and four percent of adults worldwide. Yet accurate diagnosis can be challenging, and medical options for helping these patients remain limited. Food allergies present in various fashions and widely available testing is of limited usefulness, confounding patients and their primary care physicians. Confirming the diagnosis often involves procedures like controlled food challenges or multiple endoscopies to check for esophageal inflammation. Furthermore, food allergies diagnosed in early childhood appear to be increasingly persistent into late childhood or adulthood. Media attention and general confusion has blurred the line between food allergies and food sensitization, resulting in some people living unnecessarily on difficult-to-follow diets, while at the same time others run the risk of hospitalization or death due to an undiagnosed food allergy.

Understanding and treating the growing and complex problem of food allergies requires a coordinated program of translational research and multidisciplinary care to elucidate new methods for diagnosing and treating these diseases. This need, says Aubrey Katz, MD, a pediatric gastroenterologist in the MassGeneral Hospital *for* Children (MGH*f*C) Division of Gastroenterology and Nutrition, will be met through the services of the new Mass General Food Allergy Center, which will integrate patient-centered research and evidence-based multidisciplinary practice to provide the best possible care now and in the future.

Continued on page two

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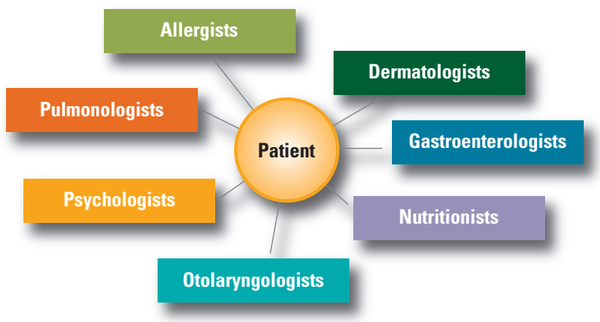
NEWSLETTER TO PHYSICIANS **WINTER 2011**

Comprehensive Food Allergy Program *continued from page one*

Multidisciplinary Clinical Care for Children, Adolescents and Adults

According to pediatric allergist Wayne Shreffler, MD, PhD, Director of the Mass General Food Allergy Center, the program is unique in that it is a comprehensive, coordinated effort by specialists in pediatrics and adult medicine, who address all food allergies, including IgE-mediated food allergy (e.g., immediate, potentially anaphylactic reactions to milk, egg, peanut, etc.); IgE-associated diseases (e.g., eosinophilic gastrointestinal disorders, atopic dermatitis); and other immune-mediated reactions to food (e.g., food protein induced enterocolitis). Patients with known or suspected food allergy are evaluated and treated by a team of providers including allergists, gastroenterologists, nutritionists, and psychologists. Additional specialists including dermatologists, pulmonologists, and otolaryngologists are also brought in as appropriate. Multispecialty clinics currently meet twice monthly at the main campus. Over the next 12 months, the program will expand to offer additional pediatric and adult clinics at MassGeneral Hospital *for* Children and in community locations. If you are interested in this clinic's availability in your area, please contact Jule Frechette at 617-643-1808 or jfrechette@partners.org.



As part of their care, Food Allergy Program physicians perform specialized testing, including skin prick tests and atopy patch testing to determine the efficacy of this approach in predicting which foods are related to Eosinophilic Esophagitis (EoE). If indicated, patients undergo food challenge testing in a controlled environment to help define problematic foods or ingredients, and they receive detailed diet guidelines from qualified dieticians to help them avoid allergic reactions while maintaining a healthy diet.

> "MGH*f*C is one of only a handful of centers worldwide offering immunotherapy trials for individuals with this allergy."

Coordinated care ensures follow-up endoscopies and other tests occur promptly, while taking into consideration family plans and the child's needs.

Innovations in Diagnostics and Treatment

Data gathered in clinic supports research efforts aimed at uncovering mechanisms of allergies, thus revealing possible new treatment options. In partnership with patients and their families, researchers are building a database of symptoms, tissue, and blood samples to inform future studies as well as launching clinical studies. One study involves oral immunotherapy for children between the ages of 3 and 21 with peanut allergies. MGH*f*C is one of only a handful of centers worldwide offering immunotherapy trials for individuals with allergies.

A second study aims to further characterize EoE and to develop better tools for identifying the disease's causes. Presenting as refusal to eat, vomiting, abdominal pain, difficulty swallowing, or food impaction, EoE was not recognized until the late 1970s. In fact, as many as 15 percent of patients diagnosed with acid reflux may have EoE. Many fundamental questions about EoE have only begun to be studied, including the role of inherited mutations, whether adults with EoE have generally had the disease since childhood, and whether long-term EoE is associated with an increased risk for esophageal cancer or other diseases. This study will contribute to our understanding of EoE by following a cohort of individuals with EoE over time to characterize the disease's pathology, search for genetic markers, and better identify foods that contribute to esophagitis. A major goal is to assess the efficacy of current and novel testing for guiding diet intervention to identify less invasive means than the current gold standard of repeat endoscopic biopsies.

As an example of the effort to develop a less stressful testing approach, the MGH*f*C Food Allergy Program is working with

Continued on page seven

Are Food Allergies Over-Diagnosed?

Q&A with Wayne Shreffler, MD, PhD

Q: Are food allergies over-diagnosed?

A: A well-known discrepancy exists between the percentage of people who believe they have a food allergy (as high as 30 percent in some surveys) and those who actually do (around four percent). Part of this discrepancy comes from confusion about the difference between food allergy and other kinds of food intolerance. However, the problem has other causes as well: Many people have evidence of an allergic kind of immune response — the presence of detectable allergic (IgE) antibodies — but are not clinically allergic. This difference between the presence of immune response and actual allergy often leads to misdiagnosis, confusion, and unnecessary food eliminations.

However, even individuals who do not have food allergies are at risk for potentially severe reactions. To avoid complications and unnecessarily restrictive diets, testing should be interpreted, along with patient history, by a physician who knows the field and can help determine the appropriate timing and setting of introducing foods.

Q: Where can pediatricians turn for assistance in treating patients with food allergies?

A: Appropriate treatment of pediatric food allergies begins with an accurate diagnosis by an allergy specialist. Pediatricians referring a patient with a known or suspected food-related problem to the MGH*f*C Food Allergy Program know that their patient will receive prompt, comprehensive, and individualized care from a multidisciplinary team of specialists.

While many questions about the causes and best treatments of food allergies remain unanswered, the combination of history taking, testing, and food challenges — sometimes involving both an allergist and a gastroenterologist — almost always leads to a definitive diagnosis and an effective, evidence-based treatment strategy. Availability of other team members, including a psychologist to help patients and families cope with emotional and behavioral concerns, ensures comprehensive care.

Q: How does diagnosis of EoE differ from diagnosis of other food allergies?

A: Some types of gastrointestinal allergic diseases, including EoE, are not consistently associated with detectable IgE. Evaluation of patients for these conditions is more complicated by this fact and contributes to the lack of uniform diagnostic criteria. Better diagnostic methods and treatments for these diseases is an area of active research by many groups, including our own.

Multidisciplinary Care Enhances Management of Children with Liver, Pancreatic, or Hepatobiliary Disease

In this country and abroad, pediatricians confront a rising incidence of liver, hepatic, and pancreatic disease due to obesity, drug and alcohol use, and metabolic or anatomic abnormalities. Management of any of these conditions and treatment repercussions are best accomplished by a team of specialists working cooperatively with the patient's pediatrician and family within the context of a major medical center. Yet few institutions have comprehensive pediatric liver programs, and an even smaller number offer patients an effortless transition from pediatric to long-term adult care.

The Hepatobiliary and Pancreatic Program at MassGeneral Hospital *for* Children (MGH*f*C Liver Program) provides this focused, comprehensive, multidisciplinary care for infants, children, and adolescents with hepatobiliary or pancreatic disorders. Because MGH*f*C operates within one of the world's foremost academic medical centers, the MGH*f*C Liver Program draws from a range of specialized expertise to provide patients the most current diagnostic and care approaches as well as seamless care from initial diagnosis through adult care.

The MGH*f*C Liver Program, under the direction of Uzma Shah, MD, comprises outpatient and inpatient services, research, and education while maintaining a warm, personalized care experience for patients. The program brings together MGH*f*C's specialists who have extensive experience in common and rare disorders of the hepatic and pancreatic system; advanced imaging technology; clinical and basic research; and participation in global health studies to effectively diagnose and treat patients using current knowledge and to continuously create safer and more effective therapies.

Uzma Shah, MD, Director of the MGH*f*C Liver Program, consults with a patient

The cross-institutional, multidisciplinary Liver Support Service provides a readily available resource base consisting of experts from hepatology, gastroenterology, surgery, transplant surgery, endoscopy, interventional radiology, liver and vascular radiology, pathology, infectious diseases, pulmonology/cystic fibrosis, immunology, hematology/oncology, psychiatry, genetics, nutrition, social work and child life, as well as nurse practitioners and transplant coordinators. These experts provide support across inpatient and outpatient services, all coordinated with one call to 888-644-3211.

Specialized Outpatient Clinics

Designated multidisciplinary clinics held weekdays at MassGeneral Hospital *for* Children in Boston and at various community locations meet the needs of patients with any type of hepatobiliary or pancreatic disease. Collaborative care of these patients includes the patient's pediatrician and family members, who are considered valuable members of the care team, and involves physicians, nurse practitioners, and nurse assistants. If needed, relevant experts from the Liver Support Service contribute to patient management.

A second clinic, held three times per month at the MassGeneral Hospital *for* Children Transplant Center, oversees the care of pediatric patients awaiting a new liver or who have undergone transplantation. In addition to their core clinical team, liver transplant patients are regularly seen by hepatologists with expertise in transplant medicine, infectious diseases specialists and transplant surgeons.

Multidisciplinary Inpatient Care

Patients admitted to the hospital receive patient-focused, multidisciplinary care in a setting that is welcoming and comfortable to children and their families. As with patients seen in an outpatient setting, the MGH*f*C Liver Program team members work synergistically with parents and primary care providers to develop and deliver treatment plans that incorporate the needs and input of those most committed to the child's health and well being. MGH*f*C Liver Program specialists serve as either attending physicians or as consultants to ensure any patient admitted with a GI disorder has access to expert hepatobiliary and pancreatic care.

Over the next year, the MGH*f*C Liver Program will expand inpatient services to include a dedicated service for children who have undergone liver transplant at MGH*f*C. As part of the Massachusetts General Hospital Transplant Center, the MassGeneral Hospital *for* Children Transplant Center will draw on the expertise and experience of the institution that established New England's first liver transplant program in 1983 and the world's first successful tolerance induction program in 1998.

Mass General surgeons provide high quality, personalized care

Advancing Knowledge and Treatment

In addition to caring for today's patients, the MGH*f*C Liver Program prepares to meet the future needs of children with these diseases by building education and research efforts. Dr. Shah and her colleagues developed a pinnacle program to train medical students, residents, gastroenterology fellows, nurses, and nurse practitioners in every aspect of care for patients with diseases of the liver, pancreas, and related structures. These educational efforts, explains Dr. Shah, include CMEs and Grand Rounds throughout the community. The MGH*f*C Liver Program is also preparing to launch a web-based teaching initiative in the near future.

The program emphasizes basic scientific and clinical research that contributes to understanding in this rapidly advancing field. Efforts under way include a study to assess an imaging alternative to liver biopsies and development of a registry for liver disease that will help inform future research into genetic underpinnings of these diseases and targeted therapies. Another, which is approaching readiness for clinical trial, involves a hepatitis B treatment trial drug.

Both educationally and scientifically, the program benefits from involvement with global experts in hepatobiliary diseases. This involvement includes collaborative research, program development, and policy formation to accelerate patient care for these complex and challenging disorders.

Information/Patient Referrals

If you would like more information about the MGH*f*C Liver, Hepatobiliary and Pancreatic Program, please call 888-644-3211.

If you would like more information about the MGH*f*C Liver Transplant Program, please call 888-644-3211.

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NEWSLETTER TO PHYSICIANS **WINTER 2011**

MGH*f*C Research:
Protecting Neonates from Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) causes devastating morbidity and mortality among premature infants. With higher numbers of women giving birth later in life and an increased use of fertility treatments, the incidence of premature births is on the rise. Modern neonatal intensive care is saving the lives of many of these tiny infants, which means pediatricians are treating an increasing number of patients with complications related to premature birth, including NEC. As many as seven percent of neonates with a birth weight between 500 and 1500 grams will develop NEC. About 30 percent of those afflicted will die. The rest will suffer life long gastrointestinal complications and, in as many as 25 percent of cases, neurodevelopmental delays, placing emotional and economic burden on the child, the family, and the medical system.

Despite considerable effort, NEC prevention remains elusive, and morbidity and mortality related to the disease remains unchanged (see table 1 for summary of preventative measures used in NEC). Enteral feeding may be associated with NEC development, yet neonatologists have no alternatives for infants incapable of oral nourishment. However research in the MGH*f*C Mucosal Immunology Laboratory, under the direction of W. Allan Walker, MD, has uncovered an approach that shows promise using probiotic secretions to protect neonates against the inflammatory response characteristic of NEC.

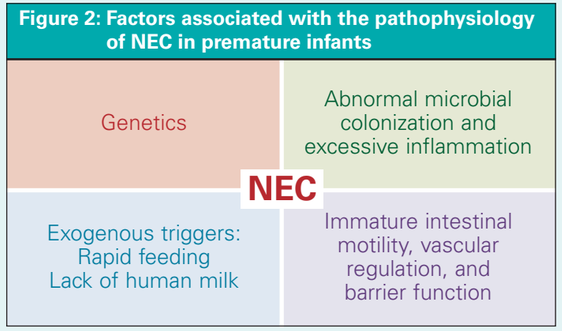
Table 1: Preventative Measures Suggested in NEC

Mother's expressed breast milk
Non-aggressive enteral feedings
Anti-inflammatory measures
- Prenatal steroids
- Postnatal probiotics
- Antioxidants – e.g., arginine

Dr. Walker's lab, which is the basic research component of the MGH*f*C Division of Pediatric Gastroenterology and Nutrition, determined that the gastrointestinal tract of infants born between 10 and 14 weeks before their due date is not sufficiently matured to respond appropriately to organisms that normally colonize the intestine and that contribute to a mature immune defense system of the intestine. During the first two weeks postpartum, as these bacteria colonize the neonate's intestine, the immune system over reacts, causing excessive inflammation that may lead to intestinal perforation and necrosis. The most common treatment is bowel resection, which is the major cause of short bowel syndrome in pediatric patients.

By comparing intestinal cells from premature and full-term infants, researchers identified differences in gene expression that trigger the immune inflammatory response. Using that information, they began investigating the usefulness of probiotics, microorganisms that stimulate the immune system. Since live organisms cannot, by law, be administered to premature infants in the United States, the researchers turned to studies in Asia and Europe, where they discovered clinical studies showing that probiotics can help prevent and lessen the severity of NEC. Dr. Walker's group grew these organisms in culture and collected their secretions. Secretions were then given to cultured fetal intestine cells to see if they had the same anti-inflammatory effect as the live organism. This process has taken nearly a decade to complete.

Figure 2: Factors associated with the pathophysiology of NEC in premature infants



Their results were positive, and the group is now identifying and characterizing the specific factor, believed to be a glycoprotein, that produces the effect. Through collaboration with the University of Chicago, Dr. Walker's lab is administering the factor to neonatal animals. If that *in vivo* trial is successful, the factor will be tested in a pilot study outside the United States and in multiple newborn intensive care units throughout South America.

"If we can show that this secreted product of the probiotic that is protective against NEC is equally as protective as the live organism," says Dr. Walker, "then we can approach the FDA about a study making this product available to premature infants in this country."

The process will take a few more years. In the meantime, the Mucosal Immunology Laboratory is working with other local hospitals to find biomarkers for NEC and producing large quantities of the product to ensure that it retains its anti-inflammatory effect when produced in bulk. Next steps will involve working with a formula company to remove any toxic substances and to lyophilize the product. If the formula retains the protective qualities, the powdered form of the probiotic secretion can be added to formula or expressed breast milk to protect premature infants from NEC until they are sufficiently matured to appropriately respond to bacterial colonization of the intestine. Identification of biomarkers will help neonatologists determine which infants need the protective additive. Until then, all premature infants below a set birth rate would receive the product in formula or combined with breast milk.

Project done by Drs. Kriston Ganguli, Nanda Nanthakumar and Allan Walker.

Left to right: W. Allan Walker, MD; Nanda Nanthakumar, PhD; Kriston Ganguli, MD

Comprehensive Food Allergy Program *continued from page three*

Gary Tearney, MD, PhD, of the Wellman Center for Photomedicine to develop a small-scale scope that can be used on an outpatient basis. When available, this tool will eliminate the need for anesthesia in patients requiring endoscopies in conjunction with food challenges.

Education and Outreach to Patients, Communities, and Industry

Another major focus of the Food Allergy Program is education for patients and family members, physicians, clinical trainees, and relevant industry representatives. Currently, Drs. Shreffler and Katz are establishing a parent advisory board to help set priorities for care, education, and research and overseeing development of a website that provides information on both IgE-mediated and gastrointestinal food allergies for patients and physicians. The program is also creating a video explaining EoE and treatment for patients and family members.

Educational programs for Mass General and community clinicians, including dieticians and nurses, are in preparation as well. These programs, including training for fellows and residents; EoE seminars for allergists and other specialists; and CMEs for primary care providers, will ensure area clinicians have the information they need to support patients on EoE or other food allergy-related diets. Community physicians calling the Food Allergy Program hotline will receive answers to their questions within 24 hours.

As part of their outreach to the community, members of the Food Allergy Program have already engaged with schools and colleges to begin developing recommendations about managing and reporting food allergies in the school setting. Recommendations will cover, for example, availability of epinephrine and policies regarding food sharing and cleaning surfaces. Other initiatives under consideration include working with hospital cafeterias to improve offerings for individuals with food allergies and meeting with the restaurant and food production industries to begin the process of identifying and labeling food to help those with allergies avoid problem foods.

To Refer a Patient

MGH*f*C allergists practice at MassGeneral Hospital *for* Children in Boston and also at MassGeneral *for* Children community locations including Newton-Wellesley Hospital and Mass General West in Waltham.

Multispecialty allergy/GI clinics meet twice per month at Massachusetts General Hospital, and the program expanded this fall to include twice-monthly clinics at MassGeneral West in Waltham.

To refer a patient, please call 617-643-6834.

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NEWSLETTER TO PHYSICIANS **WINTER 2011**

New Director of Pediatric Neurosurgery

MassGeneral Hospital *for* Children (MGH*f*C) is pleased to announce the appointment of Ann-Christine Duhaime, MD, Director of Pediatric Neurosurgery. Under Dr. Duhaime's direction, MGH*f*C's Neurosurgery Program will continue offering multidisciplinary care for children with a variety of nervous system problems while capitalizing on Mass General's unique strengths in science and technology to advance understanding of normal brain function and to optimize treatments for the disease processes that affect children of all ages. Dr. Duhaime has particular interest in the brain's response to injury as a function of maturational stage of the brain at the time the injury occurs. Currently her laboratory is involved in basic science research in this area as well as participating in a multicenter trial using instrumented helmets to study what mechanisms are linked to specific brain problems in young athletes. Clinical researchers in pediatric neurosurgery at MGH*f*C are also participating in national studies designed to gather sophisticated data on traumatic brain injury from large numbers of adults and children. Information gleaned from these studies will ultimately be integrated into stratified, multidisciplinary treatment trials for infants, children and adults with various specific types of traumatic brain injuries, as well as investigating host factors, such as genetics, which influence outcome.

For more information about the MGH*f*C Neurosurgery Program or to make a referral, please call 617-643-3399.

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