Food allergies are on the rise, for reasons that are not yet fully understood. However, there is also a tendency to over-estimate them, resulting in parents eliminating foods unnecessarily from their children’s diet. In children, adverse reactions to foods can occur by different mechanisms: Immune-mediated (IgE or not IgE-mediated); autoimmune (celiac disease) or non-immune mediated. Diagnosis of food allergy must follow well defined criteria, avoiding the many “alternative” tests currently available to the public. Non-celiac gluten sensitivity (better called Non-Celiac Wheat Intolerance) has no biomarkers available and groups a number of various possible reactions to wheat ingestion. It is a misnomer and should be abandoned in favor of Non Celiac Wheat Intolerance, itself an entity still lacking biomarkers and still not convincingly described in children.

INTRODUCTION
Adverse reactions to foods are increasing and are often attributed to allergy. Up to a third of parents report one or more food reactions in their children that they may interpret as allergies1. However, not all of these are true intolerances. Food-related disorders can lead to a spectrum of clinical manifestations and severity, only some of which are related to allergy. In fact, a true food allergy is defined as an “adverse immune response that occurs reproducibly on exposure to a given food and is distinct from other adverse responses to food”2. Other conditions causing adverse food reactions include congenital or acquired disorders of digestive-absorptive processes such as lactose intolerance, toxic or pharmacologic reactions, and autoimmune reactions such as celiac disease. Thus, the non-committal term “food intolerance” should be used to include all forms of adverse reactions due to ingested foods until an adverse reaction is proven to be due to an immune mediated process.

AUTOIMMUNE FOOD INTOLERANCE: CELIAC DISEASE
Celiac disease is the most common genetically induced food intolerance and is an autoimmune disorder affecting 1% of the population. It occurs in individuals of all ages who express the HLA-Class II haplotypes DQ2 and/or DQ8. Ingestion of gluten and related proteins found in wheat, barley, and rye trigger celiac disease in genetically susceptible individuals. It is characterized by inflammation that leads to flattening of the small intestinal mucosa. Gastrointestinal symptoms are prominent, especially in younger children, and include abdominal pain, distention,
diarrhea, constipation, and rarely malnutrition and failure to thrive. Extra-intestinal manifestations include short stature, iron-deficiency anemia, female infertility, and the typical skin finding of dermatitis herpetiformis. Diagnosis involves serologic screening with autoantibodies that are very sensitive and specific: anti-tissue transglutaminase antibodies (tTG), anti-endomysium antibodies (EMA) and deamidated gliadin peptides (DGP)\(^1\). The diagnosis is then typically confirmed by duodenal biopsies, which will show typical histologic changes in the mucosa. Celiac disease is treated by prompt and strict adherence to a life-long gluten free diet regardless of presenting symptoms.

**FOOD ALLERGY PREVALENCE**

The true prevalence of food allergies is difficult to define. The definition of food allergy is not consistent across prevalence studies. Prevalence is also influenced by whether the diagnosis was self-reported or identified by testing. These factors, as well as the fact that more than 170 foods have been identified as causing IgE mediated reactions, limit the reliability of prevalence estimates. However, a review published in JAMA in 2010 estimated that food allergy affects >1% to 2% and <10% of the US population\(^4\), and a study published in Pediatrics determined 8% of children have food allergy as identified by parental report\(^6\). It is known that self-reported allergies likely overestimate prevalence\(^8\).

In addition, there are many different types of food allergies. We will address only IgE mediated food allergy and possibly immunemediated gluten sensitivity here, try to cover others in future IMPACT newsletters.

**IGE MEDIATED FOOD ALLERGY**

A common myth in the food allergy universe is that a positive IgE test indicates a food allergy. On the contrary, it shows sensitivity to that allergen, but not an allergy. The most common food allergens in the United States include cow’s milk, egg, peanut, tree nuts, wheat, shellfish, and soy. Cow’s milk proteins followed by soybean proteins are the most common cause of food allergy during infancy, while egg protein allergy is most common in school-aged children\(^7\). Most food allergies have a high rate of resolution. About half of all children with a milk, egg, wheat or soy allergy will have resolution by age 10\(^8\). Allergies to peanuts and tree nuts are less likely to resolve\(^9\). Allergy to seeds, fish and shellfish are also considered persistent.

Why do some children develop food allergies and others escape them entirely? Risk factors for food allergy include a family history of atopy and atopic dermatitis, male gender, race/ethnicity (increased in Asian and black children compared to white children), and genetics\(^6\). Theories regarding environmental risk factors for food allergy abound, such as the hygiene hypothesis, allergen avoidance hypothesis, dual allergen exposure hypothesis, and more\(^9\). Other speculations for allergy risk factors that lack firm data include obesity, processed foods, food additives, and genetically modified foods\(^10\).

**WHAT DOES A FOOD ALLERGY LOOK LIKE?**

IgE mediated reactions to food typically occur within minutes to hours of ingestion. Different organ symptoms can be involved, including the gastrointestinal tract, skin, lungs, and heart. In children, the most common presentations are gastrointestinal, such as abdominal pain, nausea, vomiting, and diarrhea (50% to 80%), skin involvement such as erythema, itching, and urticaria (20% to 40%) and respiratory symptoms of cough, wheezing, and rhinorrhea (4% to 25%)\(^11\).

Food allergy should be suspected when symptoms occur within minutes to hours of ingestion of a specific food, especially if it occurs on more than one occasion\(^7\). Food allergy is not a typical trigger of chronic asthma or chronic rhinitis so these conditions should not prompt allergy testing\(^12\).

**DIAGNOSIS OF FOOD ALLERGY**

The diagnosis of food allergies is challenging, as there is not a uniform set of criteria to follow\(^4\). In addition to the clinical history, laboratory studies and an oral food challenge are often necessary to confirm a diagnosis. The NIAID guidelines recommend skin prick tests (SPT) and sIgE testing to assist in identifying IgE mediated food reactions. However, positive results alone are not diagnostic, so these tests should be used in the context of the clinical history and possible food challenge\(^13,14\). Physicians should be discouraged from ordering “panels” of food tests without the appropriate rationale. The gold standard for allergy diagnosis is a double-blind placebo controlled food challenge. However due to expense and lengthy time requirements, it is rarely used in clinical practice\(^20\). Both the NAS report and NIAID guidelines advice against the use of many non-validated tests, such as food allergy patch testing (atopy patch test), measurement of total IgE, and the basophil activation test, that have however gained some popularity.

**TREATMENT**

The main treatment for IgE-mediated food allergies remains avoidance of the allergen in all settings, including home, school, restaurants, and travel. Families should have a written allergy and anaphylaxis emergency plan.

**FROM CARE TO CURE**

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**PREVENTION OF FOOD ALLERGY**

Recommendations for the prevention of food allergy have changed in the past few decades. Previously allergen avoidance during pregnancy, breastfeeding, and infancy was encouraged; however these myths have been dispelled and numerous studies suggest that early oral exposure may actually
build tolerance. There is also no significant evidence for a protective effect of breastfeeding for at risk infants, although many other public health organizations promote nursing of all infants through the first 6 months of life.2,10,19

TIMING AND INTRODUCTION OF COMPLEMENTARY FOODS

There is evidence that very early (during the first 2-3 months of life) introduction of potential allergens puts infants at an increased risk for allergies. However there is no convincing data that delaying introduction of solid foods beyond 4-6 months of age has any protective effect on the development of food allergy. In the Learning Early About Peanut (LEAP) trial infants at high risk of peanut allergy (severe eczema or egg allergy) were randomized to receive or avoid peanut to the age of 5 years. The children sensitized to peanut had a peanut allergy rate of 10.6% compared to those in the avoidance group who had peanut allergy rate of 35.3% (P = .004; relative risk reduction 70%)20. The AAP, NAS and NIAID guidelines all recommend early introduction of peanuts in infants at high risk. Delaying the introduction of egg, cow milk, and wheat seems to have no benefits either.10

POSSIBLY IMMUNE-MEDIATED: GLUTEN SENSITIVITY

Gluten consumption has been linked to a wide range of disorders, including celiac disease, wheat allergy, dermatitis herpetiformis, gluten ataxia, peripheral neuropathy, and possibly this relatively new entity called “non celiac gluten sensitivity (NCGS).”

These patients by definition do not meet the criteria for celiac disease or wheat allergy, but report experiencing a number of intestinal and/or extra-intestinal symptoms after consuming gluten-containing foods. They present neither the autoantibodies nor the enteropathy characteristic of celiac disease. In NCGS, symptoms typically occur soon after ingestion of gluten-containing foods and disappear quickly after elimination of wheat-related foods. Upon reintroduction of wheat, rapid relapse typically occurs. The clinical manifestations are mostly, but not exclusively, gastrointestinal, and are similar to those of irritable bowel

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical</th>
<th>Food(s) involved</th>
<th>Diagnostic approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate GI hypersensitivity</td>
<td>Usually infancy to childhood: reactions to offending food within minutes: vomiting, diarrhea, nausea, pain; also rhinoconjunctivitis, skin rash, angioedema</td>
<td>Cow’s milk, soy, eggs, peanuts, wheat, shellfish</td>
<td>History+SPT and/or sIgE</td>
</tr>
<tr>
<td>Food protein-induced proctocolitis</td>
<td>Early infancy: streaks of blood and mucus in stools in breast-fed, typically healthy babies</td>
<td>Cow’s milk, eggs, soy, corn (in mother’s diet)</td>
<td>Clinical diagnosis supported by food elimination in mother’s diet</td>
</tr>
<tr>
<td>FPIES</td>
<td>Early infancy: vomiting, diarrhea, colitis</td>
<td>Rice, soy, cow’s milk, vegetables, fruits, oats, meat, fish</td>
<td>Clinical criteria +/- food challenge</td>
</tr>
<tr>
<td>Food protein-induced enteropathy</td>
<td>Infants and toddlers: malabsorption syndrome similar to early-onset celiac disease, hypoalbuminemia</td>
<td>Cow’s milk, occasionally soy or egg</td>
<td>Clinical diagnosis supported by duodenal biopsies with patchy villous atrophy</td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
<td>All ages: asymptomatic, reflux-like symptoms, dysphagia</td>
<td>Cow’s milk, soy, eggs, peanuts, wheat, shellfish</td>
<td>Endoscopy with biopsies</td>
</tr>
<tr>
<td>Eosinophilic gastro-enteropathy</td>
<td>Highly variable symptoms depending on localization and extension of eosinophilic infiltrates</td>
<td>Cow’s milk, soy, eggs, peanuts, wheat, shellfish</td>
<td>Endoscopy with biopsies</td>
</tr>
<tr>
<td>Gluten sensitivity</td>
<td>Mostly adults with IBS-like symptoms</td>
<td>Gluten</td>
<td>Clinical only: no diagnostic marker available</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>All ages. Strictly limited to HLA-DQ2 and/or DQ8 subjects. GI and extra-GI symptoms</td>
<td>Gluten</td>
<td>Specific serology+ diagnostic features of duodenal biopsies</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>Increases with age: abdominal pain, bloating, flatulence, diarrhea</td>
<td>Lactose</td>
<td>Clinical, breath hydrogen testing, duodenal biopsy</td>
</tr>
</tbody>
</table>

continued from page 2 >
syndrome (IBS). In 2015, one of us proposed that “NCGS is a misnomer and probably an umbrella term including various clinical entities”21. With time, it has become even more clear that this entity encompasses various, distinct populations: while a small minority may indeed react to gluten itself, the majority appear to react to FODMAPs, and among them especially fructans, as elegantly demonstrated by Skodje et al. in 201722 (See figure 1). But these patients may also react to a series of proteins found in wheat grouped under the name of ATI (Amylase-Trypsin Inhibitors)23; or to wheat with non-IgE mediated mechanisms 24; or indeed may simply respond to the placebo/ nocebo effect25. It is also important to notice that in spite of numerous reports in the adult literature, this entity has not been adequately demonstrated in children. It cannot be overemphasized how important it is to first rule out the existence of celiac disease or wheat allergy before considering NCWI.

CONCLUSIONS

Not all adverse reactions are due to food allergy, and an excellent history is the essential first step in making the proper diagnosis. The clinical history will guide appropriate testing selection. A positive sIgE or SPT alone is not sufficient to make a diagnosis – testing indicates sensitization but not necessarily clinical allergy. Finally, it is imperative to keep in mind that patient and parental reported food allergies are often not substantiated by allergy testing and may prompt investigation of other non-allergy causes of food intolerance. Table 3 Diagnostic approach for food intolerances

REFERENCES

* Division of Gastroenterology, Hepatology, Pancreatology, and Nutrition, Stead Family Department of Pediatrics University of Iowa Health Care, Iowa City, IW
**Founder, University of Chicago Celiac Disease Center and Professor Emeritus and Chief, Section of Pediatric Gastroenterology, Hepatology and Nutrition University of Chicago

In the past few years, much has been written about the risk of arsenic in rice. Because those on a gluten-free diet tend to eat more rice and rice-based products, this has been a concern in the gluten-free community. My hope is to provide some perspective and realistic recommendations for a healthy and balanced gluten-free diet.

First, what is arsenic, exactly? According to the National Institutes of Health, arsenic is a naturally occurring element.* It is fairly common in drinking water that is sourced from wells, and in food, it appears most frequently in rice and some fish. Arsenic can affect many of the body’s systems in a negative way, and can be particularly disruptive to children in early stages of development.* Children have dietary arsenic exposure from 2 to 3 times greater than that of adults and may be the most vulnerable.1 In April 2016, the FDA proposed an action level, or limit, of 100 parts per billion (ppb) for inorganic arsenic in infant rice cereal.2

A recent study found that those on a strict gluten-free diet had significantly higher arsenic in urine than those that were not avoiding gluten.3 It is important to note that arsenic in water is restricted to only 10 parts per billion (ppb). There are two types of arsenic: organic and inorganic. Organic arsenic from animal and plants is rapidly eliminated, while excess intake of inorganic arsenic, which is the type in rice, can have toxic effects.

How can you reduce the amount of arsenic you ingest through rice and rice-based products? First, try to find out where the rice was grown. Rice grown in the south-central US contains higher total arsenic concentrations compared to rice grown in California. It is believed that the higher concentration of arsenic is due to arsenic-based pesticides that were often used to treat the cotton crops in the southern United States.4 Secondly, cooking rice as if it were pasta can reduce the amount of arsenic in rice. This requires draining off the excess water, which diminishes the amount of inorganic arsenic.5 Brown rice contains more arsenic as it concentrates near the surface of the grain, which is polished to create white rice.6 However, brown rice has greater nutritional content than white rice. Look for brown basmati rice grown in India, California and Pakistan—rice from these areas has less arsenic, according to a 2015 Consumer Reports article.7

Finally, take stock of your rice intake and change up the types of grains you consume. Incorporate quinoa, millet, amaranth and teff for whole grains. Look for those with a variety of gluten-free grains. If you drink rice milk due to a dairy intolerance, try to use other types of “milks” such as soy, almond, cashew, coconut and hemp instead. Look for other sources of starch and fiber such as potatoes, tapioca, squash and corn that are typically low in arsenic. Aim to eat more colors of the rainbow and fewer processed gluten-free products for a more balanced, lower-arsenic diet.

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2 US Food and Drug Administration. Arsenic in Rice and Rice Products. Updated 2014. Available at: www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm319870.htm
5 US Food and Drug Administration. Arsenic in Rice and Rice Products. Updated 2014. Available at: www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm319870.htm
6 Signes-Pastor, A., M. Carey, and A. Meharg, Ibid.
GOING FORWARD

The University of Chicago is building a Celiac Disease Center for the 21st Century and beyond. This next critical phase will establish the Center as an international hub for clinical trials. These trials will allow the Center to follow the response to new treatments and to understand why some patients respond, and others do not. These robust studies, which will provide an understanding of the disease at the mechanistic level, are critical in applying the promise of precision medicine to celiac disease.

The University of Chicago Celiac Disease Center continues to break ground in the search for a cure. And we are closer than ever. Our world renowned experts are studying this complex auto-immune disorder from every angle to find new ways to treat and cure it. To learn more about this important effort to donate to support it, please go to www.cureceliacdisease.org.

Welcome, Dr. Rao!
The University of Chicago Celiac Disease Center welcomes Dr. Vijaya Rao to our roster of adult celiac disease experts. Dr. Rao is an adult gastroenterologist with a special interest in celiac disease and small bowel disorders. She is originally from Milwaukee, WI. She completed her undergraduate studies at Northwestern University and completed medical school and her Internal Medicine Residency at Loyola University Chicago. She subsequently completed two fellowships, in Gastroenterology and in Clinical Medical Ethics, at the University of Chicago Medicine. Dr. Rao’s research focuses on the ethical implications of invasive procedures and clinical research trials. To schedule an appointment with Dr. Rao, please call (773) 702-6140.

PARTNERS:
The University of Chicago Celiac Disease Center is required to raise its own funding, for research and programming, every year. Our partners are an important part of this effort. We are pleased to partner with the companies listed here, and we thank them for their support.

If your company is interested in partnering with us, please email us at cureceliacdisease.org/contact-us.

A Cure for Celiac Disease is possible ...

We are making it happen.

Donate Now. cureceliacdisease.org
### CALENDAR of Upcoming Events:

**SEPTEMBER 29, 2018: DR. HILARY JERICHO** of The Celiac Center will give the keynote lecture at the annual Iowa Celiac Conference, titled “Advances in Celiac Disease,” in Iowa City.

**OCTOBER 4, 2018: DR. GUANDALINI** will present: “25 years of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition: A View from a Past President” in Salerno, Italy.

**OCTOBER 27, 2018: DR. JERICHO** is an invited speaker at the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Annual Meeting Nutrition Symposium in Hollywood, FL. Her talk is on “Optimal Diagnosis and Management of Celiac Disease.”

**DECEMBER 6, 2018: DR. GUANDALINI** presents “Feeding the celiac child: yesterday, today and tomorrow,” at the Postgraduate Course “The Child between Feeding and Culture.” University of Palermo Department of Pediatrics, Palermo, Italy.

### RECENT AND UPCOMING PUBLICATIONS

In addition to all of the lectures and meetings, two publications are about to be published on research conducted at The University of Chicago Celiac Disease Center:


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### SPRING FLOORS SPRUNG AGAIN!

Once again we gathered together at Spring Flours to raise funds for the very important research going on in Dr. Jabri’s lab. This year was even more noteable as we honored Dr. Guandalini’s many years of service and long list of accomplishments at the event. The keynote speech, given by his mentee, Dr. Valentina Discepolo, was especially moving. Aside from the scrumptious gluten-free tastings of many of Chicago’s finest chefs and bakers, Spring Flours 2018 was topped off with the introduction of the Carlino family of Pennsylvania who recently made the Center’s largest-ever gift to establish and endow The Alissa and Gianna Carlino Fellowship in Celiac Disease Research to fund a post-doctoral researcher who will be dedicated to better understanding celiac disease, developing new treatments, finding a cure and training future investigators.

For photos of this remarkable evening, please click here [https://uchicagoceliaccenter.shutterfly.com/pictures](https://uchicagoceliaccenter.shutterfly.com/pictures)
OVER THE PAST YEAR, DR. GUANDALINI, WHILE STILL ACTIVELY INVOLVED IN THE CELIAC DISEASE CENTER, HAS TRANSITIONED TO PROFESSOR EMERITUS ALLOWING HIM TO REDUCE HIS HEAVY PATIENT ROSTER AS WELL AS HIS ADMINISTRATIVE AND ACADEMIC RESPONSIBILITIES. However, lest anyone think he is in full retirement mode, think again. In addition to the travel and lectures listed above, he recently completed the following:

In May, he attended the 51st Meeting of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in Geneva, Switzerland, for a Symposium on Celiac Disease; in June, he delivered four lectures at the Pan American Symposium on Intestinal Diseases in Buenos Aires, Argentina (all delivered telematically):

**Diagnosis of celiac disease in children: a paradigm in evolution**

**How to manage celiac children after diagnosis**

**Gluten intolerance: all the evils of wheat**

**Probiotics in gastrointestinal pediatric diseases: where are we now?**

And finally, at the end of June, he traveled to Albuquerque, NM, to lecture on “All Wheat: Celiac Disease and Surroundings,” at Grand Rounds at the University of New Mexico Children’s Hospital.

On May 5, 2018, a number of Dr. Guandalini’s colleagues from Italy and the U.S. came to Chicago to celebrate his medical and academic achievements on the eve of his retirement. This honor, known in academic circles as a “festschrift,” is reserved for those who have reached the highest levels of academia. The lectures ranged from scientific presentations to reminiscences of Dr. Guandalini’s career and even his wedding. The group gathered for dinner that evening, which featured speeches by those closest to Dr. Guandalini, as well as a special cello performance by Italian cellist Andrea Nocerino.

It is clear that Dr. Guandalini has no intention of pulling back on his efforts to raise awareness of celiac disease, to educate medical professionals on how to treat it and to support ongoing research efforts. Thank you, Dr. Guandalini for your unbelievable efforts and accomplishments to further the mission of The Celiac Disease Center over the last 18 years, and we hope you make some time for well deserved rest and relaxation.