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Rostrum

Should wheat, barley, rye, and/or gluten be avoided in a 6-food elimination diet?

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Eosinophilic esophagitis (EoE), a food antigen–mediated disease, is effectively treated with the dietary elimination of 6 foods commonly associated with food allergies (milk, wheat, egg, soy, tree nuts/peanuts, and fish/shellfish). Because wheat shares homologous proteins (including gluten) with barley and rye and can also be processed with these grains, some clinicians have suggested that barley and rye might also trigger EoE as a result of cross-reaction and/or cross-contamination with wheat. In this article, we discuss the theoretical risks of cross-reactivity and cross-contamination among wheat, barley, and rye proteins (including gluten); assess common practices at EoE treatment centers; and provide recommendations for dietary treatment and future studies of EoE. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Eosinophilic esophagitis, 6-food elimination diet, wheat, cross-reactivity, gluten*

Eosinophilic esophagitis (EoE) is an immune-mediated clinicopathologic disease of the esophagus that manifests as vomiting, feeding difficulties, and food impaction, which vary as a function of a patient's age. Histologically, EoE is marked by esophageal

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Abbreviations used
CEGIR: Consortium of Eosinophilic Gastrointestinal Disease Researchers
EoE: Eosinophilic esophagitis
6FED: Six-food elimination diet

eosinophilia that is unresponsive to proton pump inhibitor therapy.[1] A series of studies suggest allergic sensitization to food or aeroallergens underlies EoE.[2] Food elimination diets have been shown to be effective in achieving both clinical and histologic remission in patients with EoE,[3-10] providing evidence that EoE is, at least in part, food antigen mediated.[11]

In a retrospective study of children with EoE, Kagalwalla et al[4] found that the empiric elimination of 6 foods commonly associated with food allergies (cow's milk, wheat, soy, egg, nuts, and fish) significantly reduced esophageal eosinophilia in 74% of the patients. Dietary elimination of the same foods in subsequent prospective and retrospective studies also resulted in clinical and histologic remission in both adult[5,9] and pediatric[6,7] patients with EoE.

Kagalwalla's "classic" 6-food elimination diet (6FED)[4] is understood to technically eliminate 8 foods/food families: milk, wheat, soy, egg, tree nuts, peanuts, fish, and shellfish. Of the foods in the classic 6FED, wheat was identified as the most common trigger of EoE in adults[5] and the second most common trigger in children[12] in 2 US studies using food reintroduction to identify food antigens associated with EoE. Of foods in a "6FED-like" diet, wheat was also the second most common antigen associated with EoE in adults in a Spanish cohort.[8] Overall, wheat reintroduction reactivated EoE in 26% to 60% of patients in remission from dietary therapy.[5,8,12] Thus eliminating dietary wheat is necessary for remission in a significant number of patients with EoE. However, the extent to which wheat (and perhaps wheat-related grains) should be avoided for clinical and histologic remissions in patients with EoE remain unclear.

Wheat is a cereal grain composed of 4 fractions of proteins (ie, albumins, globulins, and "gluten" [gliadins and glutenins]),[13] any of which might elicit an IgE-mediated allergic response.[14] Wheat can be grown, harvested, stored, and/or processed with other grains, thereby contaminating these grains with wheat protein fractions.[15,16] In most countries, food allergen labeling regulations do not mandate that food manufacturers disclose cross-contamination risks on food labels.[17] Thus, patients advised to eliminate wheat on the classic 6FED might unintentionally consume trace contaminants of wheat when consuming other grains, especially grains at high risk of cross-contact with wheat, like barley, rye, and oats.[16]

In the absence of studies quantifying the clinical relevance of trace ingestions of wheat in patients with EoE, some clinicians have advocated a risk-averse approach. Prompted by concerns of wheat cross-contamination of barley, rye, and oats,[16] Doerfler et al[18] recently suggested that elimination diets for EoE be expanded from wheat free to exclude wheat, barley, rye, and conventional oats in practice to mitigate "unforeseen" risks of wheat contaminants to patients. Because wheat, barley, rye, and their crossbreeds are the only foods that inherently contain gluten, this recommendation effectively suggests eliminating all gluten-containing grains in the 6FED.

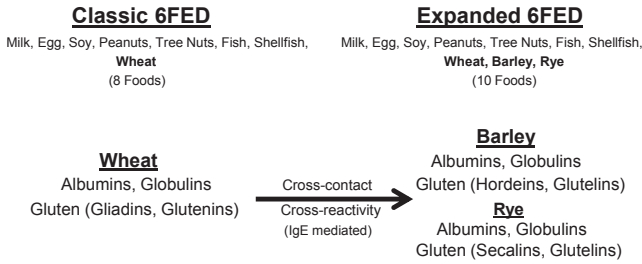

FIG 1. Classic 6FED for dietary management of EoE modified to exclude all gluten-containing grains. Uncertainty about the risks posed by cross-contamination and cross-reaction of barley and rye with wheat have led some to expand the classic wheat-free 6FED to exclude wheat, barley, and rye.

In addition to concerns of wheat cross-contamination, concerns of possible cross-reactivity among related grains (barley, rye, and wheat) have also recently led other clinicians to exclude all gluten-containing foods in empiric elimination diets.[10] Barley and rye share homologous proteins with wheat, including the "gluten" proteins hordein (barley) and secalin (rye).[19] Several studies indicate wheat, barley, and rye also share cross-reacting proteins,[20-22] which might be of relevance in IgE-mediated disease. However, in an early study of cross-reactivity of cereal antigens, only 4 of 25 patients with wheat allergy clinically reacted to barley or rye.[21] In contrast, Pourpak et al[23] found 55% of pediatric patients with IgE-mediated hypersensitivity to ingested wheat clinically reacted to barley. A strong correlation between wheat and barley serum-specific IgEs was also observed, suggesting antigen cross-reactions.[23] Studies of cross-reactivity of food antigens in patients with EoE are lacking. However, the frequency of sensitization to cereal allergens with identifiable cross-reacting aeroallergens was found to be high (63%) in a study of adults with EoE,[24] suggesting the potential for cross-reactivity among ingested grains.

To date, there are no studies to indicate whether clinical or histologic outcomes in patients with EoE would improve if the classic wheat-free 6FED was broadened to exclude all gluten-containing grains (Fig 1). To assess active ongoing practices, we queried a set of leading US clinical centers treating EoE selected by their participation in the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR), which is part of the National Institutes of Health–sponsored Rare Disease Clinical Research Consortium (http://rdcrn.org/cegir). CEGIR investigators, as well as a subset of other US-based EoE clinical practices, primarily excluded only wheat in the 6FED (Fig 2). However, a similar polling of EoE-treating international sites revealed that exclusion of all gluten-containing grains occurred more often (Fig 2). Concern over cross-reactivity of barley and rye with wheat was the most often cited rationale for eliminating all gluten-containing grains in the 6FED. It is interesting to speculate that in addition to a heightened concern about grain cross-reactivity, the reason for the difference in practice between the United States and other countries could also simply be a practical matter. In most countries outside the United States, food allergen labeling laws mandate disclosure of all gluten-containing grain ingredients (wheat, barley, and rye) on food labels. In the United States only wheat must be identified by name.[17] Thus in the United States, eliminating barley and rye adds additional burdens of label reading to identify derivatives of these grains (eg, malt from barley),[25] perhaps making

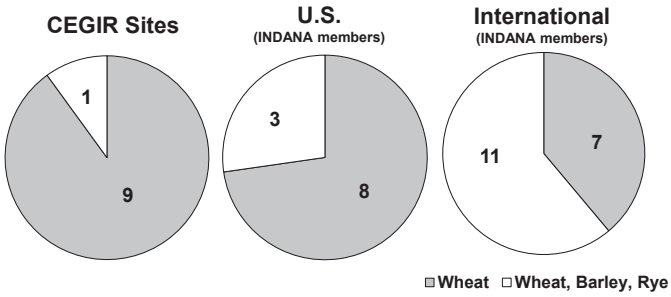

FIG 2. Survey results of the CEGIR clinical sites and dietitians in the International Network for Diet and Nutrition in Allergy *(INDANA)*. Survey response: Which foods (wheat, barley, and/or rye) do you advise patients with EoE on the empiric 6FED to avoid in your current clinical practice? CEGIR sites include Lurie Children's Hospital of Chicago; Cincinnati Children's Hospital Medical Center; Northwestern University Feinberg School of Medicine; Riley Hospital for Children/Indiana University Health; Tufts Medical Center; University of California, San Diego; University of Colorado School of Medicine & Children's Hospital Colorado; University of North Carolina School of Medicine; University of Pennsylvania Perelman School of Medicine; and the Children's Hospital of Philadelphia. INDANA (http://www.indana-allergynetwork.org/) is an international network of dietitians whose goals include developing evidence-based guidelines for diagnosing and treating patients with adverse reactions to foods, including patients with EoE.

elimination of all gluten-containing grains more difficult to accomplish in practice than in other countries. However, it is possible that even in the United States, with the growing popularity of voluntarily labeled gluten-free products, many patients avoiding wheat can avoid all gluten-containing grains. In most countries, excluding all gluten-containing grains adds additional economic burden to patients,[26,27] and product substitutes are often limited in availability (eg, breakfast cereals without barley malt).[26-28] Because the clinical "cross-reactivity" among gluten-containing grains has not been studied in patients with EoE, whether these additional burdens on patients are necessary remains debatable.

There is clearly some uncertainty about the necessity of avoiding rye and barley in addition to wheat in elimination diets in adults and children with EoE. Published and unpublished data from our centers and others (including studies of patients with EoE and gluten-triggered celiac disease) are too limited to speculate whether total gluten elimination (wheat, barley, and rye) might be meaningfully more efficacious than elimination of only wheat in patients with EoE. Unless the theoretic risks of wheat, barley, and rye cross-reactivity/cross-contamination are confirmed with empiric evidence in patients with EoE, we advise against extending wheat elimination to include the exclusion of other gluten-containing grains. Therefore, we support the continuation of the original 6FED (milk, wheat, egg, soy, nuts and fish) by Kagalwalla et al,[4] which is technically an 8-food elimination diet (with division of nuts into peanut and tree nuts and extension of fish to include crustaceans) but not a 10-food elimination diet (that extends wheat to rye and barley) until this is addressed in future studies. These future studies should ideally include clinical trials to validate dietary tools that measure intake and avoidance of wheat, barley, and rye and assess the efficacy of a 10-food elimination diet in rescuing 6FED nonresponders. If such trials indicate clinically significant rescue efficacy, studies focusing on avoidance of all 3 grains, followed by sequential reintroduction and appropriate endoscopies to confirm clinical reactions, can be conducted to predict clinical cross-reactivity risks among wheat, barley, and rye in patients with EoE. Research to identify biomarkers for food-specific EoE triggers will continue to remain important, a finding that could reduce the need for endoscopies to identify food antigens in patients with EoE.

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