Pushing the Gluten-free Envelope: First Steps Towards Evidence-based Gluten-free Diet Recommendations

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See ''A Quantitative Assessment of Gluten Cross-contact in the School Environment for Children With Celiac Disease'' by Weisbrod et al on page 289.

Even the most strict gluten-free diets are unlikely to be truly 100% gluten-free (1). Prior literature has defined safe thresholds of gluten exposure for individuals with celiac disease that have helped guide the Codex Alimentarius recommendation for the international gluten-free safety cut-off of 20 ppm (mg/kg) (2,3). Although it is clear that people with celiac disease should never knowingly eat gluten-containing foods, the risk and amount of exposure to gluten from day-to-day life (such as in a shared kitchen or at school) is unknown (4,5). Though well-intentioned, the current recommendations of avoiding all potential sources of cross-contact (however, small) may breed a culture of hypervigilance (6). Without clear evidence for safe school-based practices, this hypervigilance may extend to school-time activities. Many parents and children worry about gluten exposure during school, the potential uncomfortable and embarrassing symptoms caused by cross-contact, as well as possible long-term medical complications of poor adherence to the gluten-free diet (7,8). This fear can ultimately lead to social isolation and decreased quality of life. With over 1 in 100 school-aged children now affected by celiac disease, we desperately need better evidence to guide parents and educators on school policies (9).

In this issue of the *Journal of Pediatric Gastroenterology and Nutrition*, Weisbrod et al test common school projects by examining gluten transfer during common activities that use wheat-based products including Play-doh, baking chocolate chip cookies, paper mâché, and cooked or dry pasta at a sensory table. Gluten transfer was measured by rubbing gluten-free bread on the participating children's hands and on activity surfaces after completing the activity both before and after an assigned cleaning method. This was done to emulate performing a school activity with gluten-containing products and subsequently eating a gluten-free snack or lunch. Gluten content was quantified using a R5 sandwich ELISA. Observed gluten transfer was less than 20 ppm for both Play-doh and dry pasta. Baking chocolate chip cookies resulted in almost always greater than 20 ppm transfer of gluten onto the children's hands and the baking surface, although this was preventable with thorough hand- and surface-washing techniques. The paper mâché and cooked pasta projects also resulted in a high likelihood of greater than 20 ppm transfer of gluten to the child's hands. Although this amount of ingested gluten would be potentially harmful to children with celiac disease, it is of minimal risk if not ingested. Thus, for a child with celiac disease who is developmentally able to appropriately wash his or her hands after projects and before eating, as well as refrain from ingesting materials like Play-doh while playing with them, some commonly restricted activities may actually be safe. By identifying common school activities with high versus low risk of gluten contamination, we are better informed to make evidence-based guidelines and 504 plans to not only help parents and educators protect children from substantial gluten exposure but also prevent unnecessary exclusion from safe activities.

This article parallels the authors' recent publication in *Gastroenterology* that examined cross-contact in common food preparation scenarios and suggested that the use of a shared toaster, knife, and pot with adequate cleaning practices may be safe for children with celiac disease on a gluten-free diet (10). This study does not suggest that people with celiac disease should seek out higher risk situations or intentionally eat gluten but rather provides some reassurance that occasional small potential exposures may not be as clinically significant as we have long feared. As degree of gluten sensitivity may be variable among those with celiac disease (2,11), these groundbreaking studies are the first step in defining safe yet pragmatic gluten-free practices. Ultimately, a better understanding of cross-contamination risks may lead to less hypervigilance and improved quality of life. Updated, evidence-informed education on the gluten-free diet can lead to less confusion for families and more comfort that their children can participate in all activities, with only necessary modifications taken.

For many years, the question asked with celiac disease is ''How strict is strict enough?'' but perhaps it is equally important to ask ''How strict is too strict?'' Although this remains an exciting era for pharmacotherapeutics in celiac disease, perceived celiac disease treatment burden remains higher than many other chronic diseases, and we cannot wait for a new therapy to improve our patients' quality of life (12). Continued evaluation of the gluten-free diet and risk of cross-contact is warranted for the development of evidence-based school guidelines and to improve the psychosocial burden of celiac disease.

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Trough Measurements of Infliximab: The Earlier the Better?

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See ''Trough Levels of Infliximab at Week 6 Are Predictive of Remission at Week 14 in Pediatric Crohn s Disease'' by Courbette et al on page 310.

Therapeutic drug monitoring (TDM) is revolutionising the way we use biologic therapies within inflammatory bowel disease (IBD) allowing both dose optimisation and the personalisation of treatment to individual patient needs. Although the majority of teams would measure reactive levels at the point of loss of response, common clinical practice now is established by studies, which support the proactive measurement of infliximab (IFX) trough levels at week 14 following a standardised infliximab induction regime (weeks 0, 2, and 6 with 8-weekly maintenance) (1,2).

As an example, one of the largest studies in over 1600 IBD patients of all ages (the personalised anti-tumour necrosis factor therapy in Crohn disease, or 'PANTS' study) identified week 14 IFX levels as a predictor of subsequent clinical course. Low-drug concentration at week 14 was associated with primary nonresponse and immunogenicity, and a week 14 IFX level of 7 mg/L was demonstrated to be associated with a greater likelihood of week 14 and week 54 remission (1). Despite this knowledge, however, many paediatric patients fail to achieve 'therapeutic' week 14 levels on standard dosing regimen, prolonging the duration of active disease and increasing morbidity (3). Previously published work from our group showed that half of patients postinduction did not reach a ''conservative'' level of 3 mg/L on standard induction dosing (3). The specific target IFX level to achieve disease remission at week 14 within different patient populations and indications still remains an active research topic; however, this also raises the question: could clinical course and response to IFX be predicted sooner during the induction period?

There is emerging evidence demonstrating the association of earlier (ie, week 6) IFX levels with remission of disease in adult patients (4–6) but less so within paediatric populations (7). The retrospective study by Courbette et al (8) aims to decrease this knowledge deficit.

Courbette et al studied 111 children retrospectively with active luminal Crohn disease with the vast majority (106) receiving a standard induction regime of infliximab with a median PCDAI of 35 (interquartile range (IQR) 25–45) at treatment initiation.

The study replicated the findings of other published work that low-serum albumin and poor growth at baseline were both associated with worse clinical outcome post-induction using a multivariate analysis on this retrospective cohort.

Normal albumin levels at induction were associated with higher infliximab levels at week 6 ($P = 0.01$). Trough levels measured at both week 2 and week 6 were shown to be higher in patients deemed responsive to infliximab; and at week 6, children who failed to respond had a significantly lower median infliximab level than those with a partial or complete response (4.1 μg/mL [IQR 1.0–13.4], 6.5 μg/mL [IQR 3.7–11.5] and 11.6 μg/mL [IQR 9.1–20.1] respectively; $P < 0.01$).

The most novel finding from the study was the identification of a week 6 IFX trough level of >8.3 μg/mL as a predictor for week 14 clinical remission (sensitivity 81%; specificity 61%). Of note, this only applied to patients with luminal disease. Within the 33 patients who had perianal disease, a much higher week 6 trough level of 20.1 μg/mL was identified to be associated with improved perianal outcomes.

Currently, although there is still no universal consensus, common practice within many IBD teams (including our own) would aim for a week 14 infliximab trough level between 5 and 10 mg/L for typical patients with active luminal Crohn disease. The suggested week 6 threshold of >8.3 μg/mL identified in the present study would, therefore, seem a little conservative in this regard. The value in the present study does fit with the previous findings of Ungar et al (IFX level >7.2 μg/mL at week 6 predictive of clinical remission; sensitivity 72%, specificity 68.5%), which was a retrospective study carried out at a similar time to the Courbette et al (7) study. However, the relatively conservative nature of this value is challenged by a prospective study published in the *Journal of Pediatric Gastroenterology and Nutrition* earlier this year suggesting a much higher dose 3 (week 6) cut off of >18 mg/L. This higher trough level was associated with better clinical outcomes postinduction and was also predictive of a subsequent dose 4 trough level of >5 mg/L (9).

Additionally, an IFX level of >10 μg/mL at week 6 has been found in 2 further adult studies to promote early endoscopic healing (5,6); an important marker of disease control not analysed within the present study, and which would also be a suitable primary endpoint instead of disease activity scores, albeit somewhat difficult to perform in paediatric studies.

The present study also highlighted a different reference range for patients with active perianal disease, recognising a much higher threshold for improved clinical outcome (20.1 μg/mL at week 6). This fits with other published work, which has identified that a week 14 level of >10 μg/mL is associated with improved perianal outcomes suggesting it is important for clinical teams to identify the correct therapeutic range dependant on the primary indication for treatment.

So earlier is likely to be better with ultimately, earlier IFX level measurement allowing more efficient adjustment of dosage and consequently earlier attainment of therapeutic levels, clinical

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