A North American Serologic-based Celiac Disease Diagnosis: If Not Now, Then When?

To the Editor: In the January issue, Husby et al (1) published new ESPGHAN guidelines (last updated in 2012) for Celiac enteropathy diagnosis. The new clinical approach still uses immunoglobulin A antibodies against tissue transglutaminase (TTG-IgA) greater than 10 times the upper limit of normal as sufficient for diagnosis, with a welcome change that includes removing the suggestion of obtaining HLA genotyping to confirm their diagnosis. This decision was based on both prospective and retrospective studies, which all replicated and confirmed the 2012 guidelines and showed that the high serologic tests have >98% positive-predictive value (PPV) of enteropathy.

The Europeans have now updated their celiac disease diagnostic guidelines twice, within 1 decade. The currently posted NASPGHAN guidelines were last updated in 2005 (2). Since that time, several North American patient cohort studies have provided evidence supporting the practice of serologically based, nonbiopsy diagnosis. Our 2016 large cohort study (3) had over 500 biopsy-proven subjects and showed similar PPV and false-positive results of TTG-IgA to the ESPGHAN studies also providing a shared decision-making model for gastroenterologists. Another study from Canada supports ESPGHAN's guidelines and also demonstrated no difference in gluten-free diet adherence in those diagnosed serologically versus those with biopsies (4).

Especially now, in the current model of medicine with overpriced medical costs, poor insurance support for deductibles, and value-driven care incentives, NASPGHAN members should strongly consider adopting the ESPGHAN guidelines for nonbiopsy diagnosis. This approach provides a shared decision-making model for families, cost reduction, and a more unified, consistent approach for this relatively common autoimmune disorder.

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Lack of Correlation of Mean Corpuscular Volume to White Blood Cell Ratio to Thiopurine Levels

To the Editor: Kandavel et al (1) retrospectively investigated the value of mean corpuscular volume to white blood cell (MCV/WBC) ratio as estimates for 6-TG levels, and further as surrogate marker for thiopurine efficacy in pediatric inflammatory bowel disease (PIBD) patients treated with thiopurine in their center. Their analysis was based on 440 PIBD patients with complete blood cell count, 441 patients with ESR or CRP values, 111 patients with physician global assessment (PGA) evaluation, but only 53 patients with 6-TG levels available. No information on concomitant drugs, endoscopic findings or disease activity scores like the wPCDAI were given. The MCV/WBC ratio was poorly related to ESR and CrP and not significantly associated with the 4 categories of PGA. The concluding AuROC analysis showed poor results for prediction of quiescent disease (defined by normal PGA and ESR or CrP) by either MCV/WBC (n = 107) or 6-TG (n = 14!). In spite of these findings and major limitations of the study as pointed out in the Editorial by Bousvaros (2), the authors conclude ''that the MCV/WBC ratio provides an accurate, easy, and low-cost alternative method for therapeutic monitoring of thiopurine medications.''

To test the reliability of MCV/WBC as ''a poor man's drug level'' for thiopurine efficacy, we analyzed data from the PIBD registry of the Society for Paediatric Gastroenterology of German-speaking countries; *www.gpge.eu*). The registry includes data on more than 5000 children and adolescents with IBD with >50,000 documented contacts reported by >50 PIBD outpatient clinics from 2004 onwards.

From this registry, we obtained complete data from 226 patients with similar inclusion criteria as in Kandavel's study (first 6-TG level at least 60 days after start of thiopurines, ages 2–24, if multiple values per patient, first was obtained). Median age was 14 years (SD ± 3.34), 54% were boys, 64% had Crohn disease, and 30% ulcerative colitis.

We did not find a significant relation of the MCV/WBC ratio and 6-TG levels in our cohort or if stratified by disease activity (Fig. 1). In addition, MCV/WBC ration and 6-TG-levels were independent of biological co-medication, type of diagnosis (ulcerative colitis or Crohn disease), and sex (data not shown).

Accordingly, we could not confirm a relation of physician global assessment (PGA) with 6-TG levels (n = 226), whereas MCV/WBC ratio tended to be higher in patients judged to be in remission by the physician compared with those with active disease in a larger cohort with follow-up data (n = 1996; Fig. 2A and 2B, respectively).

As the MCV/WBC ratio is influenced by many factors including iron deficiency, steroid use, or disease activity but unrelated to thiopurine use, we investigated the distribution of MCV and WBC in relation to PGA in 1996 PIBD patients from our registry.

Figure 3 illustrates that low MCV (<72 fl) and high leucocytes (>10G/l) is significantly more common in patients with higher disease activity, indicating that the finding by Kandavel et al is an epiphenomenon of inflammatory activity, rather than reflecting low 6-TG level.

In conclusion, our data from a much larger cohort of PIBD patients with informative data clearly show that the

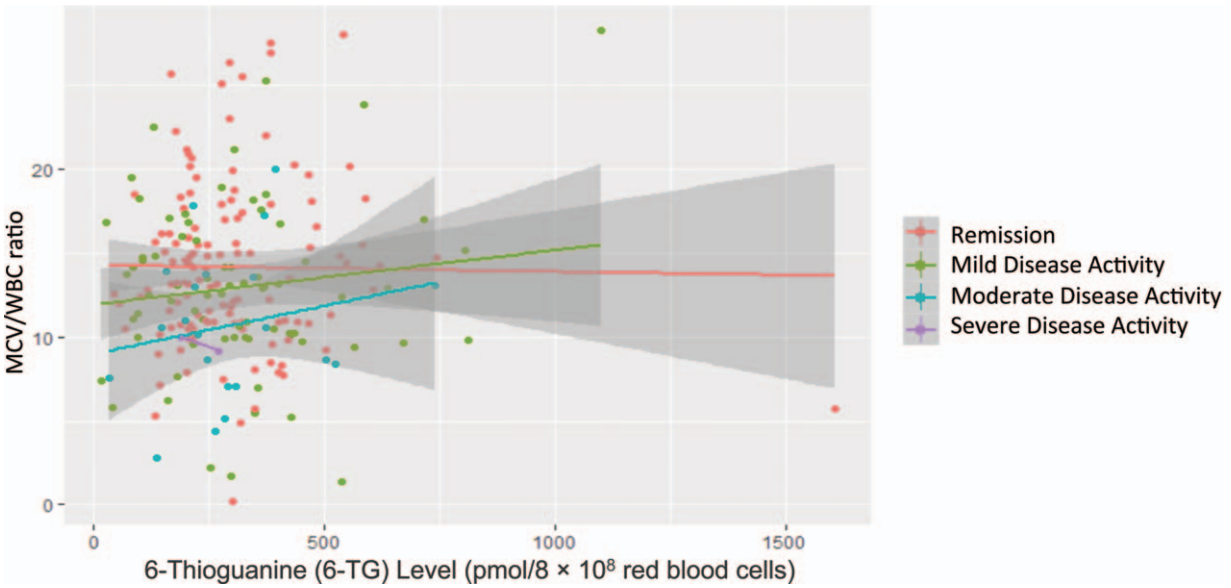

FIGURE 1. Scatterplot and linear regression for mean corpuscular volume to white blood cell ratio versus 6-thioguanine (6-TG) levels grouped by physician global assessment at next appointment—no significant correlation can be found.

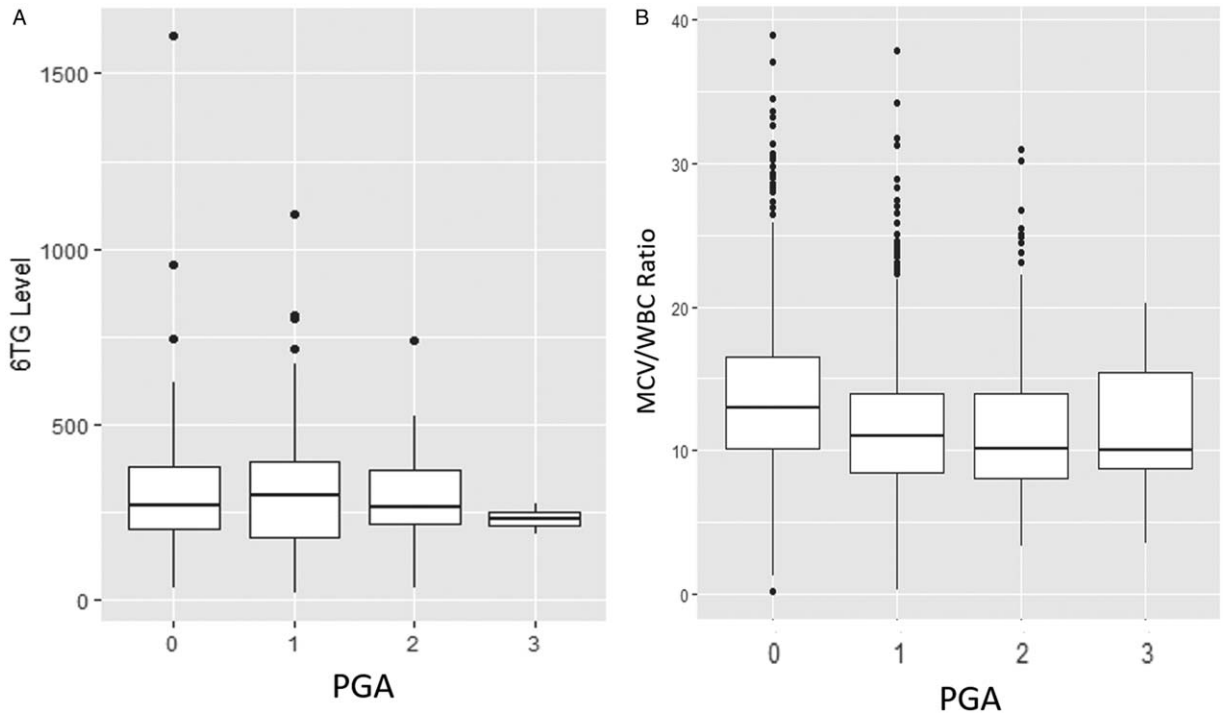

FIGURE 2. Boxplot of 6-thioguanine (6-TG) (A) and mean corpuscular volume to white blood cell ratio grouped by physician global assessment.

MCV/WBC ratio is not related to the TG-6 concentrations, and therefore, cannot substitute the measurement of metabolite levels in thiopurine-treated patients. The weak inverse correlation between the MCV/WBC ratio and disease activity is unrelated to medication. Thus, the MCV/WBC ratio is also unreliable to assess disease activity. Instead, validated scores like the wPCDAI or PUCAI or measurement of fecal calprotectin should be applied to assess a patient for quiescent disease.

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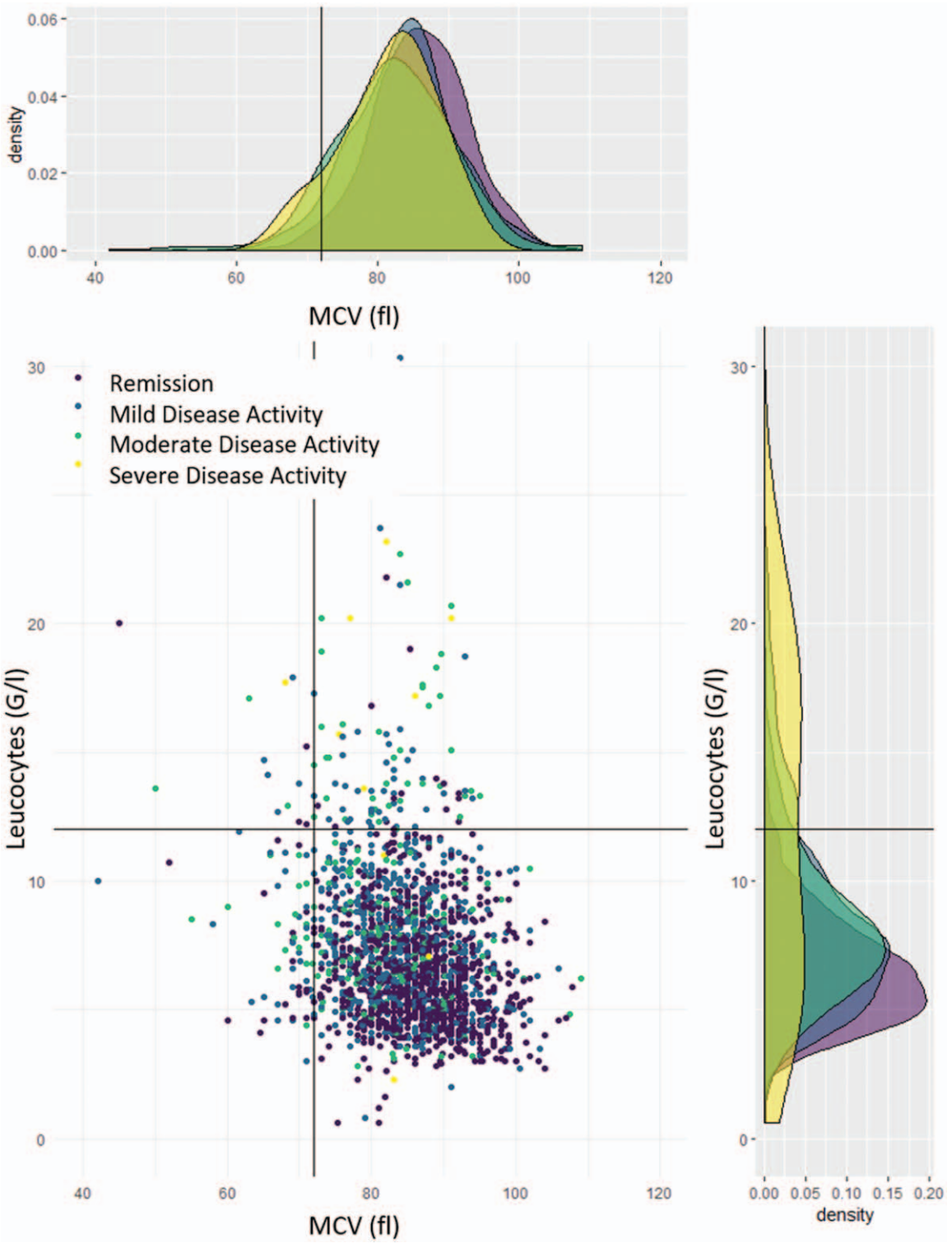

FIGURE 3. Scatterplot of 1996 pediatric inflammatory bowel disease patients in CEDATA GPGE MCV versus leucocytes, grouped by physician global assessment at next visit (remission = purple; mild disease = blue; moderate disease = green; severe disease = yellow). The different group characteristics are demonstrated by density plots linked to the *x*-axis (MCV) and *y*-axis (leucocytes). MCV = mean corpuscular volume.

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Response to Letter on ''Lack of Correlation of Mean Corpuscular Volume to White Blood Cell Ratio to Thiopurine Levels'' by Dr de Laffolie

To the Editor: We appreciate Dr de Laffolie and colleagues' interest in our study (1,2). The authors made several important points we feel should be addressed.

They evaluated 226 pediatric patients with inflammatory bowel disease, and found there was no significant association between the mean corpuscular volume to white blood cell (MCV/WBC) ratio or 6-thioguanine (6-TGN) levels and physical global assessment (PGA) (2). This corroborates the findings from our study and is consistent with other literature that has demonstrated poor predictive valuate of 6-TGN levels in thiopurine drug monitoring (3).

Dr de Laffolie, et al recommend use of the pediatric Crohn disease activity index (PCDAI), pediatric ulcerative colitis activity index (PUCAI), or fecal calprotectin rather than PGA to assess disease activity. We agree with the need for objective markers of mucosal healing for comparisons. However, neither PCDAI nor PUCAI are reliable surrogates for mucosal healing (4). Unfortunately, neither de Laffolie's nor our study had access to fecal calprotectin or endoscopic assessments of mucosal healing. We attempted to mitigate this limitation by using a combination of PGA and erythrocyte sedimentation rate and C-reactive protein as a crude, but more objective, assessment of disease activity. Admittedly, this is not ideal but this is likely better than using PGA alone. The need for information on mucosal healing remains a key limitation that must be addressed, ideally in a prospective study to validate our findings.

Dr de Laffolie raised the important question about the impact of iron deficiency, which is known to cause red blood cell microcytosis (5). To address the effect of anemia on the reliability of the MCV/WBC ratio in predicting disease activity, we reanalyzed the 471 patients included in our study. We found the MCV/WBC ratio was more reliable in predicting disease activity in nonanemic patients (hemoglobin >12.5 g/dL) with an area under the receiver operating characteristic curve (AuROC) of 0.674. In comparison, anemic patients had an AuROC of 0.584. We thank Dr de Laffole et al for pointing this out. As clinicians would recognize, microcytic anemia is often associated with ongoing disease activity, and obviates the need for such surrogates as MCV/WBC ratio (6). Therefore, the MCV/WBC ratio is most relevant to nonanemic patients, in whom the performance is better than reported in our original study (2).

As we noted, and as was reinforced by both Drs de Laffolie and Bousvaros, our findings need to be replicated in a prospective study in which mucosal healing information is available as an objective outcome measure (1,2,7).

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