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**Conflicts of interest**

The authors disclose no conflicts.

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**Reply.** We thank the authors for their interest in our randomized trial comparing endoscopy and surgery for pseudocyst drainage. All patients screened for participation in our study had a computed tomography (CT) scan that was reviewed by a dedicated expert in body imaging. The study cited by Talukdar and colleagues where CT could detect necrosis in only 23% of patients was actually conducted at our institution in Alabama nearly 16 years ago.<sup>1</sup> Since then, the quality of CT imaging has significantly improved. In the most recent study from South Korea that compared CT and magnetic resonance imaging (MRI), none of the patients diagnosed with necrosis were missed by either modality although MRI correlated better with clinical outcomes.<sup>2</sup> The limitation with CT imaging was that it overestimated the severity grading in almost all cases. The presence of debris within a fluid collection is estimated (rather incorrectly) based on Hounsfield units. In our study, more than 40% of patients were excluded as they had necrosis based on CT imaging. None of these patients at endoscopic ultrasound had necrotic debris. It is possible that some patients in the surgical cohort had liquefied necrosis that was managed by only cystogastrostomy but none required intraoperative debridement. The relevance of minimal debris in the clinical management of pancreatic pseudocysts is unclear.

We agree with the comments that the acuteness or chronicity of pancreatitis is more relevant than that of the fluid collection itself. Twenty-nine of 40 (72%) patients in this study were recruited from outpatient clinics and others as inpatient admissions or transfers from outside hospitals. While almost all outpatient enrollments had documented, long-standing chronic pancreatitis, with the exception of three cases, we are unsure about disease chronicity in 8 (20%) other patients.

The objective of the randomized trial was to compare 2 different standards-of-care techniques, surgery vs endoscopy. None of the patients undergoing surgical cystogastrostomy routinely have preoperative endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography to assess for ductal integrity and is not considered standard-of-care. As surgeons do not request pancreatic duct stent placement prior to cystogastrostomy to manage duct leak, the need for assessment of ductal integrity in uncomplicated pancreatic pseudocysts is unclear. We opine that routine evaluation of the ducts prior to surgery would be an academic exercise with limited practical utility. The single patient who failed treatment in the endoscopy cohort had inadequate drainage with transmural stenting and not a persistent pancreatic duct leak as this had resolved with transpapillary stenting.

In the United States, most surgical cystogastrostomy procedures are currently being performed via the open approach and not laparoscopy. We agree that a laparoscopic approach has lower morbidity and possibly expedites hospital stay but would also increase the cost of surgery.

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The authors disclose no conflicts.

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## Non-Celiac Wheat Sensitivity Is a More Appropriate Label Than Non-Celiac Gluten Sensitivity

Dear Sir:

We have read with great interest the article by Bieskirski et al,<sup>1</sup> in which a double-blind, placebo-controlled (DBPC) rechallenge study demonstrated a lack of evidence of specific or dose-dependent effects of gluten in patients with non-celiac gluten sensitivity (NCGS) while on a low FODMAP diet. The authors themselves noted that these data are inconsistent with their previous study,<sup>2</sup> and considered the strict control on the patients' diet throughout the entire study a pivotal difference. During the new study, all patients consumed a diet including foods with low FODMAP content and this led to an immediate improvement of the irritable bowel syndrome (IBS) symptoms, irrespective of the successive gluten challenges.<sup>1</sup>

Although we agree that FODMAP consumption can play an important role in determining IBS-like symptoms, we would like to underline some factors that merit further consideration and research. First: a major change in dietary habits modifies the intestinal microbiota and it is well known that this can be crucial in IBS pathogenesis;<sup>3</sup> future studies should also consider the microbiota, and not only the FODMAP content, in evaluating the results. Second: in a previous paper we found that about one-third of IBS patients improved on elimination diet and worsened on DBPC

challenge with wheat and cow's milk proteins,<sup>4</sup> and suggested that a percentage of them could suffer from non-IgE-mediated food allergy. However, the great majority of the patients we studied showed intra-epithelial inflammation in the duodenal mucosa (Marsh 1 lesion), a criterion considered "of exclusion" in the Biesiekirski's study.<sup>1</sup> Thus, 2 different patient populations with NCGS were studied and the results cannot be compared. However, since mucosal inflammation is a characteristic of intestinal allergic diseases, and Marsh 1 lesion can be present in several conditions other than celiac disease, we would suggest not excluding patients with duodenal lymphocytosis from future studies. Third: it is of interest that 37% of the patients recruited in the Biesiekirski's study had elevated values of serum IgA anti-gliadin antibodies. This value is greater than those reported in IBS patients, and in the absence of other reliable markers, supports a possible role of serum anti-gliadin antibodies assay in suspecting NCGS. Fourth: we were intrigued that Biesiekirski and colleagues found the highest percentage of patients reacting to the DBPC challenge in the group of those who consumed whey proteins as placebo.<sup>1</sup> Although the patient selection greatly differed from ours,<sup>4</sup> the described reaction to the whey proteins is consistent with the very frequent association between wheat and cow's milk sensitivities which we have reported.<sup>4</sup> The lack of reproducibility of the reaction to whey proteins during the second DBPC challenge, observed by Biesiekirski et al,<sup>1</sup> could be due to the short-term administration (3 days) of the whey proteins. Very delayed reactions to food antigens have been described, with symptom onset between 7 and 26 days after the beginning of the challenge.<sup>5</sup>

We thank Biesiekirski and colleagues for their important study and hope they agree that non-celiac wheat sensitivity (NCWS)<sup>4</sup> is now a better label than NCGS and that NCWS more accurately describes patients with different clinical presentations and different pathogenesis. Any label can be used but the puzzle is complex.

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The authors disclose no conflicts.

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**Reply.** The letter from Carroccio et al<sup>1</sup> raises several important issues and we will address them in sequence. First, it is likely that the 2-week run-in period during which FODMAPs were reduced<sup>2</sup> may have led to changes in the microbiota of the intestine, as recently reported after 4 weeks' exposure to dietary restriction of FODMAPs.<sup>3</sup> It is possible that such changes may be one reason for a loss of a positive response to gluten. However, it must be stressed that the role of microbiota in the pathogenesis of irritable bowel syndrome is speculative. What is good and what is not, and whether changes are secondary or primary to intestinal conditions remain to a large extent unresolved for most intestinal conditions rather than being established as 'crucial'. We agree that microbiota should be one part of the puzzle to be teased out in studies in which diet is being manipulated.

Secondly, we have difficulty with the suggestion that patients with evidence of immune activation in the duodenum should be included in a study of non-celiac gluten sensitivity (NCGS). Such changes might represent celiac disease or hypersensitivity reactions to wheat-associated proteins in some patients. The current definition of NCGS encompasses the exclusion of both celiac disease and immune responses to wheat proteins.<sup>4</sup> Given the early stages in our understanding of the NCGS entity, we believe we should strictly keep to this definition to ensure findings do not overlap with other conditions. We do agree, however, that a study with similar design to ours should be directed towards the patients with duodenal intraepithelial lymphocytosis as this is a different group to those with normal duodenal pathology.

Thirdly, we also have problems with the proposal that our data suggest circulating antibodies to whole gliadin could be a biomarker for patients with NCGS. While they were detected in one-third of the patients in our study, it is untenable to use this test as a biomarker for NCGS when none of the cohort studied demonstrated specific symptomatic reactions to gluten. In fact the opposite seems more logical. We trust we have not misconstrued the meaning of the suggestion made.

Fourthly, as evidenced by our study design, we too were concerned that we had identified patients who had reactions to whey proteins. However, all the positive reactions occurred within the first two days of exposure and very few were specific to whey. In the second challenge, it would be anticipated that reactions to a similar dose of whey would occur again quickly, especially if immune reactions are the basis for the symptom induction. It is important also to point out that the rate of placebo responses is a major difference between our findings,<sup>2,5</sup> and observations of other groups<sup>6</sup> with those in published reports from Carroccio et al.<sup>7</sup> We find placebo responses commonly in contrast to