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## Answer to Carmona R.: Are the anti-CdtB and anti-vinculin antibodies really ready for use in patients with diarrhea in Mexico? Regarding microscopic colitis<sup>☆</sup>



### Respuesta a Carmona R.: ¿Están realmente listos los anticuerpos anti-CdtB y antivinculina para emplearse en pacientes con diarrea en México? A propósito de la colitis microscópica

*To the Editors:*

We appreciate the interest of Carmona<sup>1</sup> in our article,<sup>2</sup> but it is very important to make some clarifications in response to his comments.

First, one must recognize his excellent and detailed description of the steps that must be taken for validating a diagnostic test.<sup>1</sup> However, we wish to reiterate that our brief communication<sup>2</sup> was not a validation of the anti-CdtB and anti-vinculin antibodies -which has now been published by Pimentel et al.,<sup>3</sup> but rather, as Dr. Carmona himself stated at the beginning of his letter,<sup>1</sup> simply the presentation of our clinical experience with these antibodies at a private practice in Mexico.<sup>2</sup> In fact, our experience shows findings similar to those of the previous validation,<sup>3</sup> and our data also concur with those of Remes-Troche et al. in a much larger study in Veracruz.<sup>4</sup> The latter compared the results of 339 patients with Rome III irritable bowel syndrome (IBS) vs 274 controls, finding that these biomarkers were more prevalent in IBS-D and IBS-M, with significantly elevated levels only of anti-vinculin, indicating that this marker has greater importance in IBS in Mexico, and thus requiring further investigation.<sup>4</sup>

Second, the Rome criteria for diagnosing IBS-D, which have been universally accepted for the diagnosis of IBS in all the subtypes,<sup>5</sup> is criticized. Indeed, the recently published Mexican Consensus on Irritable Bowel Syndrome, of which Carmona is the main author, establishes the following for IBS diagnosis: "The diagnostic symptom-based criteria enable the positive diagnosis of IBS in those patients without alarm symptoms and without risk factors."<sup>6</sup> To the best of our knowledge, the Rome criteria ARE the available symptom-based criteria, and in addition, they are updated based on the evidence at hand, now resulting in the publication of the new Rome IV criteria.<sup>5</sup> The same consensus states: "There is insufficient evidence for recommending a standard group of diagnostic tests in all patients meeting the symptom-based IBS criteria" and it then says: "It is recommendable to carry out complementary diagnostic tests in all patients that meet the symptom-based IBS clinical criteria and that present with alarm symptoms, refractory symptoms, or risk factors."<sup>6</sup> Therefore, there is explanation that defends the statement that "colonoscopy with biopsies should be carried out in many of the patients with IBS-D".<sup>1</sup> Does "many" refer to the majority? We imagine that it refers to those patients with IBS-D that present with alarm symptoms, refractory symptoms, or risk factors, as recommended in the Mexican consensus on IBS,<sup>6</sup> but most definitely they are not the majority. In this sense, we did not intend to report our experience with the use of anti-CdtB and anti-vinculin in patients with alarm symptoms, or those that were refractory to treatment for IBS, or with risk factors for cancer of the colon, but rather as an initial test in patients with abdominal pain and diarrhea,<sup>2</sup> who precisely -according to a group of specialists surveyed in Mexico- have at least a 61.7% probability of having IBS-D.<sup>7</sup> Furthermore, the presence of a positive test showed us that it served as a positive inclusion biomarker for IBS-D or IBS-M in the patients with the Rome III criteria for those disorders.<sup>2</sup>

Third, it should be mentioned that the Rome Foundation also recently published the multidimensional clinical profile for characterizing patients with functional gastrointestinal disorders in all their dimensions, and this profile not only includes the Rome criteria as the first category, but also physiologic markers and biomarkers as one of the dimensions, when they are available.<sup>5</sup> These 2 categories should be complemented with the clinical modifiers, symptom impact, and psychosocial modifiers to determine a diagnosis and

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individualized treatment.<sup>5</sup> Therefore, the validation of anti-CdtB and anti-vinculin as a first positive biomarker for IBS-D or IBS-M is an effort that should be welcomed and reaffirmed.<sup>3</sup> Nevertheless, we would like to know what Dr. Carmona proposes as a diagnostic method for IBS-D or IBS-M, if he considers that the Rome criteria do not have sufficient sensitivity and specificity and that positive biomarkers such as anti-CdtB and anti-vinculin are insufficient, as well.<sup>1</sup> We are certain that colonoscopy with biopsies will not be the first-line study, and by no means in young patients with no alarm symptoms. In fact, the Rome algorithms only recommend first intention colonoscopy when there is unintentional weight loss, nocturnal symptoms, a family history of colon cancer, and bloody stools.<sup>8</sup>

In relation to microscopic colitis (MC), it is typically a disease that increases with patient age, is very infrequent in patients under the age of 40 years, and is the cause of one in 10 cases of unexplained diarrhea in patients above 70 years of age.<sup>8</sup> In contrast, as has been found in Mexico, IBS is a disease in a younger population, with a mean age of  $36.9 \pm 8.8$  years in patients with IBS-Rome III that visit a gastroenterologist at the national level,<sup>9</sup> or  $41.2 \pm 14$  years in epidemiologic studies in the community using the same criteria.<sup>10</sup> In addition, even though IBS-D and MC can be associated, colonoscopy with biopsies is not indicated in all patients that present with IBS-D symptoms.<sup>5,8</sup> In accordance with these recommendations, Carmona previously reported that MC presented in 18% of consecutive patients with IBS-D seen at his private practice within a 2-year period, for which he suggested the systematic use of colonoscopy with biopsies.<sup>11</sup> It is interesting that Dr. Carmona utilized the Rome III criteria to diagnose his patients with IBS-D.<sup>11</sup> Moreover, he found no differences between patients that had Rome III IBS-D with and without concomitant MC (55.3 vs 56.4 years).<sup>11</sup> Even though some of his patients were over 50 years of age, colonoscopy with biopsies was not justified in all of the patients, given that the age range was from 20 to 89 years.<sup>11</sup> Nor did he analyze the prevalence of MC in the patients with IBS-D according to different age groups to determine whether there was a higher frequency of MC with the increase in age.

Finally, in another study in Mexico, Rubio-Tapia et al. also reported a mean age of  $56.5 \pm 15.7$  with a range of 25 to 85 years at the time of MC diagnosis, but 85% of those patients presented with weight loss (alarm symptom) and a high frequency of abnormal laboratory tests, data that, from the start, make it necessary to rule out an organic disease different from IBS and that do justify colonoscopy with biopsies in this specific group of patients.<sup>12</sup>

## Conflict of interest

In the last 12 months, Max Schmulson has received research funds from Alfa Wassermann. He has been a Member of the Advisory Board of Alfa Wassermann and Commonwealth Diagnostics International Inc, in Mexico. He has been an Advisor for Commonwealth Diagnostics International Inc, Senosiain, and Takeda Mexico. He has been a Speaker for Commonwealth Diagnostics International Inc, Mayoli-Spindler, and Takeda Mexico.

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