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**Reply to “Management of Patients with Suspected or Confirmed Antibiotic Allergy”**

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**Palabras clave:** Síndrome de enterocolitis mediado por fármacos (DIES). Alergia a fármacos. Alergia a antibióticos. Reacción de hipersensibilidad a fármacos.

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*To the Editor:*

We read with interest the article by Paño-Pardo et al [1] on behalf of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Allergy and Clinical Immunology (SEAIC), the Spanish Society of Hospital Pharmacy (SEFH), and the Spanish Society of Intensive Medicine and Coronary Care Units (SEMICYUC), which was published in the Journal of Investigational Allergology and Clinical Immunology (JIACI) in September 2022.

We are grateful to the authors for this publication, which aims to formulate evidence-based recommendations to help improve the management of patients with suspected or confirmed antibiotic allergies. However, we consider it important to make a point about section number 3.2.2. (“Can antibiotic allergy be ruled out in some patients with self-reported antibiotic allergy by means of clinical assessment? In which patients?”), where the text indicates that “patients in whom the detailed drug allergy history is conclusive of non-immune-mediated drug adverse effects, such as nausea, vomiting, diarrhea, headache, or paresthesia, can be delabeled, and further specialized evaluation or testing is not necessary”.

The categorical indication that the presence of isolated vomiting or diarrhea rules out an immune-mediated origin and, therefore, does not warrant an allergology study excludes cases of drug-induced enterocolitis syndrome (DIES).

DIES is a rare and poorly known type of non-IgE-mediated drug hypersensitivity with isolated digestive involvement that resembles that of food protein-induced enterocolitis syndrome (FPIES). It is characterized by vomiting within 1 to 4 hours after ingestion of the culprit drug and absence of classic

IgE-mediated allergic skin or respiratory symptoms, accompanied by at least 3 of the following criteria of Van Thuijl et al [2]: (1) a second episode of repetitive vomiting after ingestion of the same drug; (2) repetitive vomiting episode 1 to 4 hours after ingesting a different drug; (3) extreme lethargy; (4) marked pallor; (5) need for a visit to the emergency department; (6) need for intravenous fluid support; (7) diarrhea in 24 hours (usually 5-10 hours) after ingesting the drug; (8) hypotension; and (9) hypothermia [2]. DIES mainly affects children, although it has also been described in adults.

The prevalence of DIES is not well known. Data from the Allergy Unit of Meyer Children's University Hospital show that of all cases affecting children referred for suspected hypersensitivity reaction from 2014 to 2019, only 0.4% involved DIES [3]. Therefore, DIES could be considered a rare but not exceptional allergic disease that is probably underestimated.

Although cases of DIES have been reported with pantoprazole [4], acetaminophen [5], and olmesartan [6,7], most published cases of DIES are caused by amoxicillin [2,8-14].

The pathophysiology of DIES is unknown. AT cell-mediated response or activation of innate immunity was suggested for FPIES, which could occur for DIES. In some reported cases of DIES due to amoxicillin, patients tolerated phenoxymethylpenicillin, indicating that the side chain of amoxicillin—rather than the  $\beta$ -lactam ring—could be involved in pathogenesis.

A diagnostic drug provocation test should be strongly considered to confirm the diagnosis if only a single episode has occurred [2]. An abdominal computed tomography scan could help if it reveals intestinal edema during the acute phase. Increased neutrophil and methemoglobin values were found in most reported cases of DIES. Therefore, they should always be investigated. Tryptase is not useful for diagnosis. Acute treatment comprises intravenous ondansetron and fluid challenge, and early management enables rapid resolution of symptoms. Corticosteroids could be helpful, but their efficacy in DIES has not been proven.

In conclusion, we think that section 3.2.2. of the article should mention that in the case of a patient reporting vomiting or diarrhea who meets the criteria of Van Thuijl et al [2], an allergy study should be carried out to investigate DIES, since this is a potentially fatal syndrome that can cause kidney failure and hypovolemic shock.

DIES deserves greater attention among allergists, especially among professionals who work with children, and every effort should be made to improve correct recognition and accurate management.

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### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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