

## 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.

To the Editor:

We have read with interest the article of 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), that was published in the Journal of Investigational Allergology and the Clinical Immunology (JIACI) in September 2022.

We appreciate this publication, which aims to formulate evidence-based recommendations that contribute to improve the management of patients with suspected or confirmed antibiotic allergies. However, we consider it important to make a point about section number 2.2. (“Can antibiotic allergy be ruled out in some patients with self-reported antibiotic allergy by means of clinical assessment? In which patients?”), which indicates that “patients in whom the detailed drug allergy history is conclusive of non-immunemediated drug adverse effects, such as nausea, vomiting, diarrhoea, headache, or paraesthesia, can be de-labelled, and further specialized evaluation or testing is not necessary”.

The categorical indication that the presence of isolated vomiting or diarrhoea rules out an immune-mediated origin and, therefore, does not warrant an allergological 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 in the 1-4h period after ingestion of the culprit drug and absence of classic IgE-mediated allergic skin or respiratory symptoms, accompanied by at least

three of the next criteria of Van Thuijl et al.: 1) a second episode of repetitive vomiting after ingestion of the same drug; 2) repetitive vomiting episode 1–4 h/s after ingesting a different drug; 3) extreme lethargy; 4) marked pallor; 5) need for emergency department visit; 6) need for intravenous fluid support; 7) diarrhea in 24 h (usually 5–10 h) after ingesting drug; 8) hypotension; and 9) hypothermia [2]. It involves mainly children, but it has been also described in adults.

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

Although cases of DIES have been described with pantoprazole [4], acetaminophen [5] and olmesartan [6,7], the majority of published cases of DIES are precisely due amoxicillin [2, 8-14].

The pathophysiology is unknown. A T 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 the pathogenesis.

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

In conclusion, we think that section 2.2. of the mentioned article should mention that if a patient reports the appearance of vomiting or diarrhoea, who meets the criteria of Van Thuijl et al, an allergy study should be carried out to find out if it's a DIES, since it is a potentially fatal pathology that can cause kidney failure and hypovolemic shock.

DIES deserves more attention among allergists, especially among the professionals who work with children, and all efforts should be conceived to improve its 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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