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## Reply



To the Editor:

We thank Li et al<sup>1</sup> for their comments on our recent publication.<sup>2</sup> We agree with the caution that there is a possibility of drug excipient as a culprit cause in our case. Similar to Hong Kong, drug package inserts are not enforced by law to include excipient lists in Thailand. Therefore, Thai allergists confront a similar situation in practice.

The 2 formulations in both drug provocation tests were different. We wrote letters to both pharmaceutical companies, and they replied with some data on excipients (Table I). The trade name and companies' names are not disclosed because of their internal disclosure policies. Some excipients in amoxicillin-clavulanic acid were the same in both formulations used in the 2 provocation tests, but some were not. We have identified the excipients that were different between tests in bold font. The 3 different excipients in the second provocation included apricot powder, caramel powder, and mannitol. There is a possibility that these excipients could have caused an immediate hypersensitivity reaction.<sup>3,4</sup> Caramel coloring may be derived from various sources that are considered as common allergens, such as starch hydrolysates (from wheat), malt syrup (may have been derived from barley), or lactose (from milk). Our patient had no previous history of food or plant food allergy. However, he reported a history of hypersensitivity to other drugs, including clarithromycin and levofloxacin although he was unable to recall the details of these events.

We have read your interesting reports on the importance of excipient allergy in patients with immediate hypersensitivity to systemic corticosteroids.<sup>5</sup> We are well aware that complete allergy testing would increase the chance of culprit(s) identification. When dealing with a complicated situation, such as perioperative hypersensitivity, the excipients and related disinfectants have been routinely included in skin test panels since 2017 in our institution.<sup>6,7</sup>

**TABLE I.** Excipients of amoxicillin-clavulanic used in 2 drug provocation tests

|                   | First provocation<br>(negative)                                                                                                                                                                                             | Second provocation<br>(positive)                                                                           |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| Formulation       | AM-CL suspension                                                                                                                                                                                                            | AM-CL syrup                                                                                                |
| AM:CL ratio       | 200 mg:28.5 mg                                                                                                                                                                                                              | 600 mg:42.9 mg                                                                                             |
| Manufacturer      | Company A                                                                                                                                                                                                                   | Company B                                                                                                  |
| Product reference | Not available                                                                                                                                                                                                               | Not available                                                                                              |
| Excipient list    | Aspartame, colloidal silica, <b>hydroxypropyl methylcellulose</b> , <b>monosodium citrate</b> , <b>sodium citrate</b> , <b>strawberry flavor</b> , <b>strawberry guarana flavor</b> , xanthan gum, <b>FD&amp;C red "40"</b> | Aspartame, <b>apricot powder</b> , <b>caramel powder</b> , colloidal silica, <b>mannitol</b> , xanthan gum |

AM, Amoxicillin; CL, clavulanic acid; FD&C, Federal Food, Drug, and Cosmetic Act code.

Note: The excipients that were different between the 2 provocations are represented with bold font.

We could not specifically conclude the culprit in our case because we did not repeat skin tests and perform *in vitro* testing for clavulanic acid and other excipients, which were limited due to the patient's condition and medications. However, based on the likely trace amounts of excipients ingested, it would be unusual for any of them to cause a fatal reaction. Our reported case together with your valuable suggestion is a cautionary tale to allergists dealing with drug hypersensitivity. We do not have enough evidence to recommend a routine test including excipients at the first evaluation of the beta-lactam allergic patients. There is a lack of excipient skin test standardization, unknown cost utility, and the risk of cutaneous sensitization to excipients. In our opinion, we would perform excipient testing for certain drugs (eg, corticosteroids)<sup>5</sup> and cases with clinical resensitization to different manufactured beta-lactams after delabeling. We also advocate legal regulations to include excipient lists in the package inserts as a part of drug registration, which might lead to more complete allergy histories. We very much appreciate the helpful correspondence you have provided, and we thank your team for the data provided to fulfill the knowledge of drug allergy tests to allergists worldwide.

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