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Delayed hypersensitivity reactions to piperacillin-tazobactam



To the Editor:

We read with great interest Gallardo et al's¹ article recently published in *The Journal of Allergy and Clinical Immunology: In Practice* regarding immediate hypersensitivity reactions to piperacillin-tazobactam (PipTaz) confirmed by either skin or drug provocation testing. Of interest are the key identification of different immediate-type hypersensitivity phenotypes and the systematic approach to clinical diagnostic as well as *in vivo* testing. The authors also performed drug provocation tests in the 2 patients with negative skin testing to confirm the drug allergy label. However, we note that a limitation of the article is the absence of an assessment of delayed PipTaz hypersensitivity reactions, which are frequently encountered in the hospital setting.

PipTaz is frequently used in cancer care and sepsis management for empirical gram-negative bacterial coverage.² In these cases, other confounding factors could be causal for skin eruptions such as graft versus host disease, fever as well as isolated eosinophilia, in the setting of infection in the critically ill.³ Although PipTaz is implicated in these scenarios, it may not be part of causality. When looking at allergy labels in our hospital over a 12-month period (October 2019 to September 2020), among the 42,643 patients admitted, 88 (0.2%) carried a PipTaz allergy label.

To contribute to the existing literature gap on PipTaz immune-mediated reactions as underlined in a recent journal editorial,⁴ we audited our prospective database of 1715 patients with antibiotic immune-mediated reactions (between April 2015 and October 2020 with some of the cases that might have been included in previous publications⁵⁻⁷).

Among the 44 identified (26; 59% immunosuppressed), 6 had presented an immediate reaction, 35 (80%) delayed, and for 3 patients the timing could not be determined from history. In terms of drug allergy causality association with PipTaz, 15 (34%) of patients had a Naranjo score of ≥ 5 (probable) and 29 (66%) a score of 4 (possible). After allergy investigations, 16 of 44 (36%) had positive beta-lactam intradermal testing (IDT)—4 (25%) immediate

and 12 (75%) delayed—11 of 44 (25%) had positive IDT to PipTaz (2 immediate and 9 delayed). Among these 11 patients, 8 had a positive IDT to amoxicillin/ampicillin (Amox/Amp). Among the patients with positive IDT to PipTaz, 6 had a positive IDT to penicillin G. A total of 6 patients had positive testing to PipTaz, penicillin G, and Amox/Amp. Among the patients with delayed positive IDT, 8 had interferon- γ enzyme-linked immunosorbent assay performed as per previously published method,^{6,7} with 4 (50%) having a positive assay. After allergy investigations, 3 (6.8%) patients were delabeled in the allergy clinic for their PipTaz drug allergy. Our data were limited by the absence of drug provocation tests after negative PipTaz testing due to the inability to give prolonged intravenous challenges in the setting of delayed hypersensitivity.

We need further data on delayed hypersensitivity reactions in the setting of PipTaz use, especially considering that they contribute to 75% of allergies encountered in a specialist drug allergy center. In particular, we need further studies that challenge immune-mediated hypersensitivity reactions with negative *in vivo* investigations, especially in PipTaz delayed hypersensitivity, and continue to enable the use of this life-saving antimicrobial therapy.

Ana Copăescu, MD, FRCP^{a,b}

Jason A. Trubiano, BBS (Hons), FRACP, PhD^{b,c,d,e}

^aClinical Immunology and Allergy, McGill University Health Center, Montréal, QC, Canada

^bCentre for Antibiotic Allergy and Research, Austin Health, Heidelberg, Vic, Australia

^cDepartment of Infectious Diseases, Austin Health, Heidelberg, Vic, Australia

^dDepartment of Oncology, Sir Peter MacCallum Cancer Centre, The University of Melbourne, Parkville, Vic, Australia

^eThe National Centre for Infections in Cancer, Peter MacCallum Cancer Centre, Parkville, Vic, Australia.

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Corresponding author: Ana Copăescu, MD, FRCP, Austin Health, 145 Studley Rd, Heidelberg, Vic 3084, Australia. E-mail: ana.copescu@gmail.com.

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