

Prolonged Beta-Lactam Provocation Challenges in Children: Do Extended Protocols Offer Any Benefit?



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Beta-lactam allergy is overdiagnosed in the pediatric population because most children developing exanthema during beta-lactam treatment are labeled as allergic without any confirmatory workup.¹ Labeling a patient as penicillin allergic imposes a higher burden on his or her health in terms of microbial resistance patterns and treatment costs.² Although a careful history can sometimes identify patients who have experienced reactions concerning for more serious reactions, such as IgE-mediated symptoms, Stevens-Johnson syndrome, or drug reaction with eosinophilia and systemic symptoms, many patients and parents are unable to fully recall details of the timing and clinical manifestations of previous reactions to a drug.³ This complex scenario results in physicians needing to effectively assess and rule out a risk of a serious reaction on future exposure to the drug by balancing the risk-benefit ratio of testing and appropriate drug challenges. Further complicating the clinical algorithm for these patients, there is currently no consensus or guidelines regarding a protocol for how best to approach drug provocation challenges in children with a history suggesting mild nonimmediate reactions to beta-lactam antibiotics.

In this issue of the *Journal of Allergy and Clinical Immunology: In Practice*, Rodriguez et al⁴ retrospectively analyzed 97 children who were referred for a nonimmediate reaction to beta-lactam antibiotics and were evaluated through a new provocation challenge protocol. All children underwent a 1-day hospital provocation test (HosPT) and if no reactions were triggered in an interval equal to the time elapsed between the first dose and the symptoms of the index reaction, the patient continued with a home provocation test (HomPT) for an equal amount of time. Fourteen children (14.4%) had a positive reaction, 11 during the HosPT (3 immediate and 8 delayed) and 3 during the HomPT (1 immediate and 2 delayed). This study demonstrated that a delayed reaction can be triggered with a single dose of the drug. The authors suggested that although the potential time of the workup was longer than in other protocols, for some as long as 20 days, 20.6% of children needed 4 days or less and most of them (72.5%) needed 10 days or less.

There are some interesting points highlighted in the Rodriguez et al article. Of particular note, there was no skin testing or

prescreening test of any type used before the provocation challenge, and patients were selected on the basis of clinician identification of a history of nonimmediate reaction to beta-lactam antibiotics. The use of drug provocation tests (DPTs) without skin tests in children with suspicion of a history of mild nonimmediate reactions is gaining some traction in the literature, with some studies reporting successful use of DPTs in children without previous skin prick testing.⁵ Delayed reading intradermal test utility in children has also been questioned in some studies, given a low sensitivity and low positive predictive value.⁶

Two of the delayed reactions that occurred in the Rodriguez et al study also warrant further consideration. One patient experienced an event of what was considered mild anaphylaxis after ingestion of the first dose on the HomPT. Was the interval of time from the first dosing schedule of the drug enough to create a window of time for resensitization or new sensitization to the antibiotic? This is a concern and a consideration in terms of the utilization of a protocol where there is a period of non-exposure before repeat exposure. Another patient who reacted at HomPT was reported to have been ill with a febrile respiratory infection that started 1 day before starting the HomPT of the DPT. This situation underscores the importance of patients being well when they undergo these procedures; otherwise, results could be misleading or ambiguous and could expose patients to additional risks. Recently, Mori et al⁷ described a related concern in terms of sensitization to amoxicillin/clavulanic acid underlying severe rashes that develop in children treated for infectious mononucleosis. These clinical scenarios serve to emphasize the importance of careful selection and timing of challenges for patients in terms of clinical well-being at the time of DPT.

Another important consideration is the variability in length of the DPT protocol. There are many protocols published in the literature with varied lengths of provocation challenge timing, from as short as 1 day to as long as 10 days.⁸⁻¹² These studies do not suggest an interval of wait time between the initial provocation from the HosPT that correlates with the index reaction, as Rodriguez et al propose. Rodriguez et al suggest that a strength of their protocol is that it would capture some patients earlier in a shorter DPT, decreasing the length of the protocol and the number of unnecessary doses of antibiotic, while also capturing those cases that take longer to present with the option of a longer protocol.

Furthermore, immediate reactions of concern are identified on the first day of any drug test/provocation test protocol, including skin testing and/or a provocation challenge. Prolonged courses of provocation usually only identify instances of mild exanthema or urticarial rashes. There is not enough evidence in the literature or theoretical mechanisms postulated to support the concern that a precursor event of mild exanthema in the form of maculopapular exanthema (MPE) or mild urticaria predisposes a patient to future more serious delayed hypersensitivity reactions such as Stevens-Johnson syndrome, drug reaction with eosinophilia and

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systemic symptoms, or serum sickness-like reactions. Are these mild exanthema or urticaria considered a contraindication to completing the course of the drug or repeating the course in the future? If not, then one would argue that a prolonged challenge is inherently unnecessary. There is an existing risk in the general population for these mild drug rashes with or without a prolonged challenge to a beta-lactam. Moreover, as Rodriguez et al also discuss in the article, patients undergoing this time-consuming and tedious procedure have the added burden of unnecessary doses of antibiotic with potential risk of a new reaction and increased cost and time to complete such a process without an added benefit to their disease course. In addition, a recent study by Tonson et al¹³ demonstrated that in children with a previous positive DPT result, 89% had no reactions at rechallenge 3 years later and 68% of those have tolerated subsequent treatments, suggesting a natural acquisition of tolerance.

In conclusion, there are no consensus positions to date on the process of DPT protocols for mild nonimmediate reactions to beta-lactam antibiotics in children. Important considerations in establishment of a consensus protocol for DPT in children with mild nonimmediate reactions to beta-lactam antibiotics include the need for preemptive skin testing and the length of the protocol for the DPT. Rodriguez et al⁴ introduce an option for an interval period of nondosing that seems to potentially decrease the length of time and number of antibiotic doses for some patients but may pose a risk of new sensitization to the beta-lactam antibiotic through the process of the protocol itself in the dosing gap. The observations of Rodriguez et al do underscore some additional conclusions regarding DPTs for these patients. First, patients should be clinically well when undertaking a DPT procedure. Second, though varied lengths of prolonged DPT challenges have been proposed, the benefit of these protocols is questionable in terms of their contribution to improved outcomes. Finally, these cases of mild delayed exanthematous and urticarial reactions to beta-lactams in children remain an unavoidable health care burden that needs to be addressed by the Allergy community worldwide, and we remain in a position of handling each circumstance on a case-by-case

basis of risk-benefit analysis without an overarching agreement in protocol.

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