

A Much-Anticipated Leap Forward in β -Lactam Drug Allergy: Phenotyping Reactions to Piperacillin/Tazobactam



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Piperacillin/tazobactam hypersensitivity can present with a complex array of reactions, but there is a gap in the literature that relates to our understanding of most aspects of the topic. We, therefore, felt rather enthusiastic about the findings on immediate allergy phenotypes recently described by Gallardo et al.¹ However, we would like to take this opportunity to put the relevance of their observations into context.

The Global Point Prevalence Survey of Antimicrobial Consumption and Resistance,² a cross-sectional audit performed in 2015, included data from 303 eligible hospitals from all around the world. Their results showed how the most commonly prescribed antibiotics for community-acquired infections in adults were penicillins with a β -lactamase inhibitor (29.2%), including piperacillin with a β -lactamase inhibitor (7.7%). Moreover, the most prescribed antibiotics for health care-associated infections among adult inpatients were penicillins with a β -lactamase inhibitor (24.8%), including piperacillin with a β -lactamase inhibitor (14.6%).

Interestingly, it is not uncommon for patients to receive recurrent courses of piperacillin/tazobactam, and, in fact, a retrospective 6-year study of patients with reported penicillin allergy in several centers within Texas, USA, showed that piperacillin/tazobactam was the most frequently repeated penicillin overall.³

These data suggest that piperacillin/tazobactam is not only one of the most commonly used antibiotics around the world but also one of the most repeatedly used antibiotics on individual patients. This is particularly relevant because repetitive exposure is one of the most commonly recognized risk factors for drug allergy.⁴

These findings are consistent with data from Liang et al,⁵ who performed a retrospective 9-year study in several centers covering

the southern California population and included a remarkable total of 37,387,313 patient-years of follow-up. They showed how piperacillin/tazobactam had the highest number of courses within the β -lactams and, consequently, the highest rate of new allergy reports (0.93%).

Considering this, the reader might be wondering why there are virtually no feature articles on the study of hypersensitivity to piperacillin/tazobactam, almost no drug allergy guidelines focused on piperacillin/tazobactam, and merely a few articles on drug challenge or drug desensitization specifically with this drug. A simple search will provide the reader with many interesting case reports on the most unusual reactions attributed to piperacillin/tazobactam, with varying quality regarding their allergy workup. Large and well-designed studies that can help us understand the full picture of hypersensitivity to this drug are comparatively scarce.

The clinical picture of hypersensitivity to piperacillin/tazobactam is rather obscure, and it seems to vary from one population to another. In the large study by Liang et al,⁵ interestingly, the rate of anaphylaxis was surprisingly low (0.001%) when compared with other supposedly rarer reactions, such as drug reaction with eosinophilia and systemic symptoms (0.016%) or nephropathy (0.13%).

However, observations can change depending on factors such as data collection/documentation, statistical analysis, or selected population. For example, a 20-year retrospective article from Berlin, Germany, studied reactions to parenteral antibiotics given to a population of children and adults with cystic fibrosis (CF). When they focused their analysis on a nested population with at least 5 years of continuous medical records at their center, they found that piperacillin/tazobactam had the highest absolute number of reactions among all parenteral antibiotics.⁶ In contrast with data from Liang et al, in this article (with different methods and population), 88% of the reactions were immediate, and the symptoms were mainly dermatological (45%), respiratory (14%), and fever (13%), with the highest absolute number of anaphylactic reactions among all antibiotics.⁶

Piperacillin/tazobactam has been involved in all types of reactions, from severe cutaneous adverse drug reactions to nephropathy, with one article showing rates for nephropathy that were a 10-fold higher than the rate noted with parenteral penicillins.⁵ However, this antibiotic is frequently given to critically ill patients with multiple comorbidities, which makes it difficult to determine causality.⁵

The clinical assessment of many reactions to piperacillin/tazobactam is quite complex and requires a great deal of

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expertise. Dorman et al³ showed how a delabeled patient may easily regain his or her allergy label after a nonspecific reaction, or conversely how patients with seemingly classical delayed reactions to piperacillin/tazobactam, be it erythema, interstitial nephritis, or benign exanthema, may unexpectedly show uneventful tolerance to the drug after the initial reaction.

Allergists need the skills and resources to assess and manage these patients. Allergy services receiving inpatient referrals for reactions to β -lactam antibiotics might expect that up to 2% of these will be for a reaction to piperacillin/tazobactam, as was shown in a 2-year retrospective study of a drug allergy unit in London, UK.⁷ Allergy services in tertiary or specialized hospitals with special populations, such as patients with CF, might experience even higher referral rates for piperacillin/tazobactam. These can be as high as 29% of referrals, as shown in a 10-year historical cohort study performed in a CF center of Montpellier, France.⁸ As piperacillin/tazobactam is one of a limited number of antipseudomonal antibiotics available, the risks of not investigating a reaction to piperacillin/tazobactam are potentially even greater than for other β -lactams. This is particularly true, in populations such as CF, in whom adverse reactions to antibiotics are responsible for up to 65% of changes in therapy.⁶

Gallardo et al¹ have published in this journal the largest series of immediate reactions to piperacillin/tazobactam to date. They addressed the key relevance of a systematic approach to the study of reactions to piperacillin/tazobactam, including skin testing, drug challenge, and cross-reactivity study. Their study is another landmark, as it contains the only published piperacillin/tazobactam drug challenge protocol. Unfortunately, their series of cases includes only patients with a confirmed diagnosis, so we cannot fully assess the safety of this protocol, because data on their general population are lacking (total number of patients referred for a reaction to piperacillin/tazobactam, number of negative drug challenges, and so on). It is, however, encouraging that their study, spanning 10 years, reported having only 2 positive challenges. Conversely, a 5-year study by Mawhirt et al⁹ reported 2 cases of anaphylaxis during drug challenge with piperacillin/tazobactam despite negative skin tests. Even if drug challenge remains the criterion standard to rule out a drug allergy,¹⁰ it is nonetheless a potentially high-risk procedure to be carried out in dedicated spaces by experienced allergists.

The systematic approach of Gallardo et al¹ enabled them to describe 3 major phenotypes of allergic patients with confirmed IgE-mediated immediate reactions to piperacillin/tazobactam, namely: (1) sensitized to the β -lactam ring (needs to avoid β -lactams, query on skin testing and/or challenge with carbapenems); (2) purportedly sensitized to the lateral chain of aminopenicillins (might cross-react with certain cephalosporins, will need skin testing and drug challenge to select alternatives); (3) selective to piperacillin/tazobactam alone (they tolerate other β -lactams).

There is no global consensus regarding the necessary reagents for penicillin allergy testing.¹⁰ The fact that piperacillin/tazobactam can cause drug-specific reactions is important, as testing with the culprit β -lactam (in this case, piperacillin/tazobactam),

and not only with penicillin skin test reagents, is fundamental not to miss these patients.

From the therapeutic point of view, in the hands of multidisciplinary teams led by expert allergists using *in vivo* and *in vitro* validated protocols, drug desensitization is an effective tool to induce temporary tolerance to piperacillin/tazobactam in patients with a confirmed hypersensitivity.⁴ Further study on the phenotypes/endotypes of hypersensitivity to piperacillin/tazobactam will help us better select those patients in need of drug desensitization versus those suitable for drug challenge with effective alternatives.

Two recent international consensus documents developed by one of the working groups of the International Drug Allergy Symposium AAAAI/WAO 2018^{10,11} described clear unmet needs on which future research should focus, and Gallardo et al certainly tackled some of the key ones, namely cross-reactivity, optimal overall testing strategies, the adequate set of skin test reagents and concentrations, criteria for positive results, appropriate drug challenge protocols, and including well-characterized patients in real-life situations. Phenotyping and endotyping are fundamental in drug allergy, and findings like those described by Gallardo et al directly address the evolving needs of precision medicine in drug allergy, which can help us provide more personalized practical guidance for patients in future.

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