

A pragmatic approach to beta-lactam use in patients with penicillin allergy

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We read with great interest the study by Prematta *et al.*,¹ who investigated physician approaches to β -lactam use in patients with penicillin hypersensitivity and concluded that the variability in survey responses related to cross-reactivity between β -lactams showed the need for additional education, research, and improved guidelines. We discuss and share our perspectives in the following paragraphs.

In China, all package inserts of penicillins (*e.g.*, oxazocilline, amoxicillin, and piperacillin) state that prescribing these medications should be forbidden for patients with penicillin allergy as well as patients with positive skin test. However, prescribing information of other β -lactams (cephalosporins, cephamycins, oxacephems, monobactams, and carbapenems) does not list penicillin allergy as a contraindication. Physicians can prescribe other pharmacodynamically and pharmacokinetically appropriate β -lactams for patients with penicillin allergy. Of course, caution is recommended.

Our hospital is a university teaching hospital with 2200 beds and 2.5 million person-time outpatients annually. In October 2010, a standard operation procedure was established for approaches to β -lactam use in patients with penicillin allergy through team work among physicians, nurses, and pharmacists. Prescribing cephalosporins are forbidden for patients with a history of type I hypersensitivity (Gel and Combs classification) or exfoliative dermatitis induced by penicillin or a strongly positive penicillin skin test (*i.e.*, systemic responses occurred outside the injection site). With respect to patients with mild to moderate allergic reactions to penicillin, skin test should be performed

by intracutaneous injection of a sterile solution of the corresponding cephalosporin (300–500 μ g/mL) in normal saline before administration of an i.v. cephalosporin. Cephalosporin solutions for skin testing are proved to be stable for 24 hours after reconstitution if stored at 2–8°C, and presented as centralized preparation from injectable therapeutic preparations in a center of pharmacy i.v. admixture services. This cephalosporin can be given to the patient only if the cephalosporin skin test is negative. In the past two years, ~20 thousand cephalosporin skin tests were performed under the protocol, cephalosporin allergy was abolished successfully in patients who had a negative skin test with corresponding cephalosporin despite a history of mild to moderate penicillin allergy or a positive penicillin skin test (*i.e.*, raised red bump with diameter of >1 cm, or a pseudopod formation and itchy feeling around the flush). In addition, our operation pattern brings more economic benefits (*e.g.*, saving \$4000 in disposable supplies annually), lower occurrence of medical disputes related to β -lactam allergy (0.5 per million in 2011 versus 15 per million in 2009), and higher satisfaction from doctors and nurses (95.7% in 2011 versus 50.0% in 2009).

Penicillins have a cross-allergy with first-generation cephalosporins (odds ratio, 4.8) and a negligible cross allergy with second-generation cephalosporins (odds ratio, 1.1).² Skin test with cephalosporin before direct i.v. use carries less risk of cross-allergy and warrants higher safety. Our experiences may provide a pragmatic approach to β -lactam use in patients with penicillin allergy.

ACKNOWLEDGMENTS

The authors thank Jun Shou and Yan-yang Zhang for their excellent work and for the support of the Division of Medical affairs and Division of Nursing.

REFERENCES

1. Prematta T, Shah S, and Ishmael FT. Physician approaches to beta-lactam use in patients with penicillin hypersensitivity. *Allergy Asthma Proc* 33:145–151, 2012.
2. Campagna JD, Bond MC, Schabelman E, et al. The use of cephalosporins in penicillin-allergic patients: A literature review. *J Emerg Med* 42:612–620, 2012.

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Funded by the Zhejiang Provincial Bureau of Health (2012KYA090) and Zhejiang Scientific project (H20101641, H20101032, and H20100332)

The authors have no conflicts of interest to declare pertaining to this article

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To the Editor

We appreciate the comments raised by Zhu and colleagues regarding our study titled "Physician Approaches to Beta-lactam Use in Patients with Penicillin Hypersensitivity". The authors raise an important point that cephalosporins are underutilized in patients labeled with penicillin allergy, and share their institutional approach of skin testing these patients with the cephalosporin of choice. The authors have utilized this approach to determine whether cephalosporins are safe to use in patients with mild to moderate penicillin reactions, or a positive skin test to penicillin, and find that this approach is cost-effective. We agree with the authors on these points, and our study supports the concept that physicians underutilize cephalosporins in part due to lack of understanding of beta-lactam hypersensitivity. The issue of cross-reactivity between hypersensitivity to penicillins and cephalosporins continues to be a clinical problem. Although there is likely a low cross-reactivity between penicillins and cephalosporins, large prospective studies are lacking. Skin testing to a cephalosporin of choice is an option to determine whether the drug may be used safely. Concentrations of non-irritating doses of many cephalosporins have been defined,¹ and a positive skin test supports the potential of an IgE-mediated reaction. However, as skin testing is performed to the native drug, a relatively low sensitivity is expected. Thus, a negative test should be followed by drug provocation

testing to confirm a lack of sensitivity.² As the R-group side chains may play a role in cross-reactivity between penicillins and cephalosporins, an alternative approach is to choose an agent with a different R-group and perform a graded challenge to establish safety.² In the case of mild reactions that are delayed and consistent with type IV hypersensitivity reactions to penicillins, we advocate performing a challenge, either to the penicillin or the cephalosporin to be considered. In these cases of mild delayed reactions, the rash is rarely reproduced on re-administration of the implicated agent.³ In cases of severe reactions, such as Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome, there is no clear consensus about how to proceed and rates of cross-reactivity are not defined. This is an area that requires more research.

Sincerely,
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REFERENCES

1. Empedrad R, Darter AL, Earl HS, and Gruchalla RS. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. *J Allergy Clin Immunol* 112:629–630, 2003.
2. Drug allergy: An updated practice parameter. *Ann Allergy Asthma Immunol* 105:259–273, 2011.
3. Caubet JC, Kaiser L, Lemaître B, et al. The role of penicillin in benign skin rashes in childhood: A prospective study based on drug rechallenge. *J Allergy Clin Immunol* 127:218–222, 2011. □

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