

agree with his comment concerning the novelty of natural killer (NK) 2 cells in asthma. He referenced 3 publications to verify that our study is not the first article to indicate a possible role of NK2 cells in asthma. However, 2 articles focused only on serum levels of cytokines in asthmatic patients but did not do FCM and consequently cannot establish the cellular sources of cytokines.¹⁰ The other report dealt with NK2 cells in patients with atopic dermatitis (not asthma), and this was published after our report.¹¹ There is one publication closely related to our study; however, this study did not critically analyze the intracellular cytokines in NK cells. Instead, they focused on the regulation of CD95⁺ NK cells on CD40 ligand expression of T cells in asthmatic patients on the basis of CD95 expression; they called the NK subset NK2 cells.¹² Because intracellular cytokines are the most representative markers for NK1 and NK2 cells if compared with T_H1 and T_H2 cells and CD95 molecules are almost 100% positive in NK1 cells and 40% positive in NK2 cells,¹³ which are not extensively recognized as NK2 markers,¹⁴⁻¹⁶ we consider that the phenomenon of NK2 bias in asthma is first observed in our study.

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Major and minor determinants are high-performance skin tests in β -lactam allergy diagnosis

To the Editor:

As Bousquet et al¹ have commented in the Journal, major and minor penicillin determinants have been removed recently from the European market. Therefore in early 2004, we started to test major and minor penicillin determinants by using benzylpenicilloyl polylysine (PPL) and minor determinants mixture (MDM; including benzylpenicillin, benzylpenicilloic acid and sodic benzylpenicilloate, all at 0.5 mg/mL) from Diater S.A. (Madrid, Spain), which have been available on the market since 2003. In 20 patients previously given a diagnosis of penicillin allergy, we tested both Allergopen (Allergopharma, Reinbeck, Germany) and Diater determinants according to the usual protocol.^{2,3} Because we observed an optimal concordance between the 2 preparations, we continued testing our patients with Diater determinants.

Since January 2004, 463 patients have been studied for suspicion of β -lactam allergy. After written informed consent was obtained, skin prick and intradermal tests were performed with PPL, MDM, penicillin G, and the suspect drug if it was other than penicillin. If the skin test results were negative, a controlled drug challenge was performed under strict supervision. After 15 days, new skin tests and drug challenges were performed again, as the European Network of Drug Allergy recommends.³ After completing the study, 44 patients were given a diagnosis of β -lactam allergy on the basis of skin testing (6 of them in re-evaluation) and 2 on the basis of only challenge (results in Table I).

Our findings resulted in nearly half of the subjects (47%) receiving misdiagnoses, in cases in which PPL and

TABLE I. Distribution of positive skin test responses (n = 44)

	Positive test response, total (%)	Positive test response alone (%)*
PPL	20 (45.4)	6 (13.6)
MDM	24 (54.5)	7 (15.9)
PPL + MDM	13 (29.5)	8 (18.1)
PPL and/or MDM	32 (72.7)	21 (47.7)
Penicillin and/or other†	23 (52.2)	13 (29.5)

*Patients in whom these test results were the only positive results.

†Penicillin and/or amoxicillin, ampicillin, or cephalosporins.

MDM determinants are withdrawn, and being submitted to a drug challenge. Because we did not perform challenges in subjects with positive PPL or MDM skin test results, we cannot provide exact data about specificity. However, our 9.9% of positive results is similar to results seen in most published series,³ and we might speculate that specificity could be high. Because only 2 subjects had negative skin test results and positive challenge results (4.3% of the positive studies), our results support the high sensitivity and negative predictive value of skin testing. Our results with Diater determinants show different performance compared with the data of Bousquet et al.¹ We have shown that around 10% of patients have a positive study result compared with 22% in the Bousquet study, in which 136 were given diagnoses on the basis of skin tests and 53 on the basis of challenge alone. Surprisingly, only 20 patients had positive PPL skin test results, MDM skin test results, or both (14.7%)¹ compared with 72% of patients in our series. Furthermore, the efficiency-sensitivity of skin tests in our case was quite a bit higher because only 2 of 463 (0.4%) received misdiagnoses by means of skin test and then received diagnosis by means of challenge compared with 57 of 824 in the series of Bousquet et al.¹

Although both groups see different results regarding this matter in nonuniform populations, we could also conclude that major and minor determinants are the best and useful tools in the diagnosis of β -lactam allergy. We can finally conclude that new determinants commercially available in Europe are reliable and safe alternatives to Allergopen, with similar high sensitivity and, probably, specificity.

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Reply

To the Editor:

We would like to thank Matheu et al¹ for their comments. Overall, there are no major discrepancies between our study and this letter because we emphasize the importance of benzylpenicilloyl polylysine (PPL) and minor determinants mixture (MDM) in the diagnosis of β -lactam allergy.

For several possible reasons, Matheu et al¹ found a few differences within our findings. First, the population studied was badly described, and because neither of the 2 studies was carried out in the general population, large differences might exist in terms of referral of patients.

Second, antibiotic prescription varies widely between countries,² and this can account for some differences. Moreover, the delay between the reaction and testing is not presented. This point is crucial because an important number of allergic patients might have had a reaction occurring more than 20 years ago, when amoxicillin was not available. It is well known that with amoxicillin allergy, the side chain of the molecule is one of the major allergenic moieties, which is not included in PPL, MDM, or both.

Third, Matheu et al¹ tested PPL, MDM, penicillin G, and the suspected drug only if it was different to penicillin. In our study we systematically included amoxicillin and ampicillin, as currently recommended,³ because the contribution of adding amoxicillin to skin tests (ie, the percentage of patients further detected) has changed from 17.3% in 1990 to 43% in 2000 and 51.4% in 2005 in Spain (Torres MJ, Blanca M, unpublished data). In our study 29 of the 53 positive challenge results were in patients with positive results to amoxicillin.

Fourth, the reagents from Diater (Madrid, Spain) used by Matheu et al¹ are not described, and we were unable to find a study on these reagents on Medline. It is therefore scientifically impossible to compare the 2 studies, even though, in a small study involving 20 patients, the authors state that there was an "optimal concordance" between their reagents and AllergoPen.

It is, on the other hand, of great importance to be aware of the fact that such PPL and MDM reagents are available in Europe. However, more precision is required concerning their composition, manufacturing processes,