

Reply

To the Editor:

Reijmerink et al¹ raise an important issue that the association between the Toll-like receptor 4 (*TLR4*) Asp299Gly polymorphism and lower LPS-induced IL-12(p70) and IL-10 secretion reported by us² might be confounded by asthma status. Atopic asthma was by itself associated with both the polymorphism and low LPS-induced cytokine secretion.² When comparing individuals without asthma separately, the association between the *TLR4* Asp299Gly polymorphism and low IL-12(p70) release remains in our study, however (Fig 1, A), and a similar trend is observed for LPS-induced IL-10 secretion (Fig 1, B). Because of the small number of individuals, and because none of the patients with atopic asthma responded with IL-12(p70) release, the association to the polymorphism was not analyzed in the group with asthma separately. The results indicate that the polymorphism by itself is associated with impaired responses to LPS and does not just mirror the link between asthma and low cytokine release and genetic variation.

Reijmerink et al¹ illustrate their concern regarding our results with an example from their own study in which an association among the *CD14/-159* polymorphism, frequency of CD14⁺ cells, and atopy was observed.³ We emphasize that in our study, this polymorphism (*CD14/-159*) was associated with low IL-12(p70) release but not with atopy or allergic symptoms.

In conclusion, in our study, the *TLR4* Asp299Gly polymorphism is associated with asthma and independently also with low LPS-induced cytokine secretion.

Malin Fagerås Böttcher, PhD^a

Anna Lindström, MSc^a

Maria Christina Jenmalm, PhD^a

Bengt Björkstén, PhD, MD^b

Outi Vaarala, PhD, MD^c

From the ^aDivision of Paediatrics, Department of Molecular and Clinical Medicine, Unit of Clinical and Experimental Research, Faculty of Health Sciences, Linköping University, S-581 85 Linköping, Sweden; ^bCentre for Allergy Research and Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden; and ^cDepartment of Molecular Medicine, National Public Health Institute, Helsinki, Finland.

REFERENCES

1. Reijmerink NE, Hylkema MN, Postma DS, Bruinenberg M, Kauffman HF, Koppelman GH. Confounding effect of atopy on functional effects

of the *CD14/-159* promoter polymorphism. *J Allergy Clin Immunol* 2006;117:219.

2. Böttcher MF, Hmani-Aifa M, Lindström A, Jenmalm MC, Mai X-M, Nilsson L, et al. A *TLR4* polymorphism is associated with asthma and reduced lipopolysaccharide-induced interleukin-12(p70) responses in Swedish children. *J Allergy Clin Immunol* 2004;114:561-7.

3. Koppelman GH, Reijmerink NE, Stine CO, Howard TD, Whittaker PA, Meyers DA, et al. Association of a promoter polymorphism of the *CD14* gene and atopy. *Am J Respir Crit Care Med* 2001;163:965-9.

Available online October 4, 2005.
doi:10.1016/j.jaci.2005.07.030

The contribution of major and minor determinants from benzylpenicillin to the diagnosis of immediate allergy to β -lactams

To the Editor:

We would like to comment on the recent letter published by Bousquet et al,¹ which emphasizes the role of major and minor determinants of benzylpenicillin (benzylpenicilloyl polylysine [PPL] and minor determinants mixture [MDM]; Allergopen, Allergopharma, Reinbeck, Germany) for skin testing in patients with allergy to β -lactams. The withdrawal from the market of these reagents has set us back many years, and an approach based only on the clinical history might classify as false-positive many patients who are suspected of being allergic to β -lactams but who in fact have good tolerance after an appropriate allergologic workup.² According to the letter, 14.7% of the cases would have been missed if these reagents had not been used. Moreover, if we include those patients who had positive results to different penicillin determinants (and which, in some countries, are not always available) and who also had positive results to PPL, MDM, or both (32%), the number of nondiagnosed cases would have increased to 46.7%. Thus almost half of all the patients would not have received proper diagnoses if PPL and MDM had not been used.¹

Studies have shown that of patients with allergic reactions to penicillin confirmed by means of skin testing, 75% had positive results to PPL, 10% to MDM, and 14.8% to PPL and MDM.³ In our experience the contribution of PPL, MDM, or both to total skin test positivity was 42.1%,² which is similar to the results reported by Bousquet (46.7%).

The disagreement seen between groups^{1,2} reflects different patterns of β -lactam prescription and consumption that vary from country to country and even within the same country over the years. To this extent, we have shown that differences exist when analyzing populations in one country at different times,² such that the contribution of PPL, MDM, or both to skin test positivity in the 1990s was 77.7%, in 2000 was 42.1%, and in 2005 is 22.1%, as suggested by current information from our database.

In conclusion, although differences exist between countries and over time, skin testing with PPL and MDM is more necessary for the diagnosis of β -lactam allergy than suggested in the letter. An international coordinated effort under the direction of experts is necessary to provide

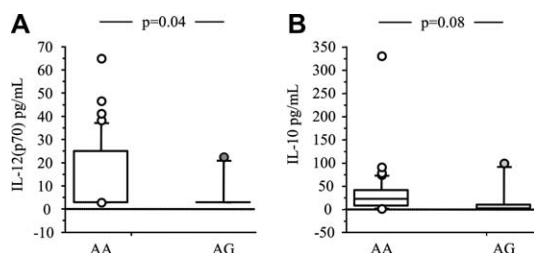


FIG 1. LPS-induced IL-12(p70) (A) and IL-10 (B) secretion from PBMCs in individuals without asthma divided into groups according to the *TLR4* (Asp299Gly) AA and AG genotype.

industry with the support required to continue producing these valuable reagents.

*María José Torres, MD, PhD
Miguel Blanca, MD, PhD*

From the Allergy Service, Carlos Haya Hospital, Málaga, Spain.
Supported by Fondo Investigación Sanitaria grant FIS PIO20666 and CIYIT BQU2001-3624.

REFERENCES

1. Bousquet PJ, Co-Minh HB, Amoux B, Daures JP, Demoly P. Importance of mixture of minor determinants and benzylpenicilloyl poly-L-lysine skin testing in the diagnosis of beta-lactam allergy. *J Allergy Clin Immunol* 2005;115:1314-6.
2. Torres MJ, Blanca M, de Weck A, Fernandez J, Demoly P, Romano A, et al. Diagnosis of immediate allergic reactions to betalactam antibiotics. *Allergy* 2003;58:961-72.
3. Gadde J, Spence M, Wheeler B, Adkinson NF Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. *JAMA* 1993;270:2456-63.

Available online October 4, 2005.
doi:10.1016/j.jaci.2005.08.012

Reply

To the Editor:

We would like to thank Torres et al¹ for their comments. We are pleased to see that we have the same viewpoint concerning the importance of benzylpenicilloyl polylysine (PPL) and minor determinants mixture (MDM) in the diagnosis of β -lactam allergy and that another study made in another country can confirm our findings.

As they mentioned, 46.7% of the patients in our study and 42.1% in their study would not have received proper diagnoses if PPL and MDM had not been used. Moreover, the proportion of patients with positive responses to PPL, MDM, or both decreases over time. Torres et al¹ suggest that 22.1% of their patients have positive responses to PPL, MDM, or both only in 2005, which is not significantly different from our data (14.7%), with an increase of the proportion of patients with positive responses to other haptens, such as the side chain of amoxicillin.

These findings reinforced our perception of the importance of PPL and MDM in the diagnosis of β -lactam allergy. Effort should be made to produce these reagents.

*Philippe Jean Bousquet, BSc
Pascal Demoly, MD, PhD*

From the Exploration des allergies, Maladies Respiratoires—INSERM U454, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, 34295 Montpellier Cedex 5, France.

REFERENCE

1. Torres MJ, Blanca M. The contribution of major and minor determinants from benzylpenicillin to the diagnosis of immediate allergy to β -lactams. *J Allergy Clin Immunol* 2006;117:220-1.

Available online September 27, 2005.
doi:10.1016/j.jaci.2005.08.013

The use of principal component analysis to explore relationships between factors

To the Editor:

As a researcher who is currently selecting validated outcome measures to include in a clustered, randomized controlled trial, it was with great interest that I read the recent article by Schatz et al.¹ The authors used principal component analysis with varimax rotation to reveal a model of 5 independent factors underlying 4 validated tools.

However, I would like to offer a word of caution regarding one aspect of their analysis: the understanding of the relationship between factors. The aim of principal component analysis is to transform a set of variables into a smaller set of variables²; their study revealed that the principal component was “symptom frequency.” However, the use of varimax rotation produces factors that are orthogonal (ie, uncorrelated).³ It is therefore not surprising that the 5 factors included in the reported hypothetical model were independent.

It would be of interest to know whether the authors conducted additional unreported analysis, such as principal axis factoring with oblique rotation, and if so, what the outcome of this additional analysis was. This latter method differentiates between unique and common factors and relaxes the rule of orthogonality. This might lead to a different model, possibly ultimately resulting in a different selection of validated quality-of-life tools in a research setting, clinical setting, or both.

Jane Upton, BSc, MSc, PhD

From the Education for Health, The Athenaeum, 10 Church St, Warwick, CV34 4AB, United Kingdom.

Disclosure of potential conflict of interest: J. Upton works for Education for Health (formerly the National Respiratory Training Centre) in England.

REFERENCES

1. Schatz M, Mosen D, Apter AJ, Zeiger RS, Vollmer WM, Stibolt TB, et al. Relationships among quality of life, severity, and control measures in asthma: an evaluation using factor analysis. *J Allergy Clin Immunol* 2005;115:1049-55.
2. Duntman GH. Principal components analysis. Beverly Hills (CA): Sage University Paper; 1989.
3. Kim J-O, Mueller CW. Factor analysis: statistical methods and practical issues. Beverly Hills (CA): Sage University Paper; 1978.

Available online October 4, 2005.
doi:10.1016/j.jaci.2005.07.035

Reply

To the Editor:

We thank Ms Upton for her letter¹ and interest in our article, “Relationships among quality of life, severity, and control measures in asthma: an evaluation using factor analysis.”² We agree that the 5 factors included in the final model should be independent on the basis of the methodology (varimax rotation) that we used. At Ms Upton’s suggestion, we performed the factor analysis using principal axis factoring with oblique rotation. We found