

Penicillin allergy is a global problem: The European experience

To the Editor:

In the article by Macy et al¹ in the May issue of *The Journal of Allergy and Clinical Immunology*, a number of statements are made that require comment.

In many countries, including the United States, France, and Spain, amoxicillin is the most commonly administered betalactam, representing more than 80% of all betalactam prescriptions.¹⁻⁵ It therefore seems reasonable to accept that amoxicillin is also the betalactam that is most commonly involved in the production of allergic reactions, whatever the study results appear to show, so that patients can be cross-reacting with benzylpenicillin or another penicillin, or having a selective response.²

Variations are seen when different studies are compared and disagreements occur when inferences are made from data obtained from each particular study and extrapolated to other populations in other countries.^{1,3,4} In general, when results are compared, we need to be cautious. In some instances, studies are performed in adults and in others in pediatric populations, and the cumulative exposure to the different betalactams during a subject's lifetime is different, both quantitatively and qualitatively.²⁻⁴ No less important is the great variability in the interval between occurrence of the reaction and patient evaluation.⁶⁻⁸ Some studies present patients who had a reaction more than 40 years before the study; at that time, consumption, in terms of chemical compound and indications, was certainly different from nowadays.^{7,8}

One of the major limitations of Dr Macy's studies of amoxicillin allergy is that he only uses amoxicillin at the maximum concentration of 2 mg/mL for both intradermal and prick testing.^{1,7,8} In our experience amoxicillin for skin prick must be used at 20 mg/mL and for intradermal at up to 20 mg/mL. However, caution is required, especially with intradermal testing, as severe anaphylactic reactions may occur at these doses. If testing is performed by experienced persons at this maximum concentration, it does not give false-positive results.² The amoxicillin used by Dr Macy comes from SIGMA and cannot be diluted at the maximum concentration recommended by us.^{1,7,8} Furthermore, this compound is not licensed by SIGMA for testing in human beings. The amoxicillin we use in Europe is the one used for parenteral administration, as it is soluble at 20 and 200 mg/mL (the latter concentration is for intravenous use). The different concentrations used for skin testing are obtained from this maximum stock solution.²

The second major issue is, as mentioned above, that Dr Macy's patients have a very long interval between the initial reaction and the allergological evaluation: 14.9 ± 15 years (range, 0 to 54.84 years).¹ We believe this is a source of important differences.

Data quoted by Dr Macy, based on the natural evolution of sensitivity, are not prospective and therefore lack accuracy because patients were initially classified as positive on the basis of clinical history, and it is agreed by all, including Dr Macy, that this is quite inaccurate. Prospective data indicate that the rate that skin tests become negative depends on the specificity of the reaction. Amoxicillin-selective patients will become negative in 5 years, and at least 30% of patients with BPO and/or MDM allergy will become negative in this period of time. Therefore even in the presence of a past positive history, evaluation based solely on clinical history is very difficult. This reference is systematically omitted by Dr Macy in his reports when he refers to the natural evolution of sensitivity.^{1,7,8}

In the Discussion section, Dr Macy makes a number of statements that we consider inappropriate.¹ He states that severe allergic reactions to oral amoxicillin are rare. However, most anaphylactic reactions reported in Spain and other countries have occurred after oral intake, especially of amoxicillin.²

We disagree with the statement that most penicillin-associated reactions may be non-IgE-mediated in subjects with negative skin test results. Data from various studies indicate that no more than 70% of subjects evaluated will have positive skin test results.⁴ In the event of a positive response, two mechanisms can explain this: either an IgE-mediated reaction or a T-cell-dependent response. Additionally, the assumption that T cells may not mediate these reactions has no scientific background, and for betalactams, it is difficult at this moment to provide an alternative explanation. Although skin tests in delayed reactions do not have sufficient sensitivity, some evidence indicates that these are T-cell-mediated responses, although further studies are necessary to support this.

The authors state that the incidence of adverse reactions during skin testing is approximately 1%. In our experience, and in that of others, it is greater than 13%.⁹ Obviously, this depends on the time interval and the population studied.

Finally, the recommendation made in the summary of the Discussion is in contradiction with what has recently been published by expert groups.¹⁰ As the *Journal of Allergy and Clinical Immunology* is the most widely read allergy journal, we believe that this statement and the entire article may lead to confusion among readers and consequently to incorrect medical decisions.

As proposed in several previous articles and reviews, we have been recommending since the beginning of the 1990s the development of common protocols and approaches to tackle this subject, which has great clinical importance. Since Professor de Weck appointed a group of experts in the ENDA network (European Network for Drug Allergy), a common approach has been accomplished after many years of critical discussions and interchange of data among a panel of investigators in this field. This has resulted in an update on the subject reflecting the European view.¹⁰ However, more work is required on both sides of the Atlantic and even the world over. As rep-

resentatives of a group involved in multidisciplinary research in this topic, with clinicians, immunologists and chemists, our attitude has long been to make available our files, clinical data, sera banks, and other biological samples to any investigator, including the pharmaceutical industry, who is concerned and willing to collaborate. If these efforts lead to improvements in our understanding and to clarifying some of the many remaining questions behind the problem of allergy to betalactams, patients all over the world will certainly benefit.

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