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REPLY

We thank our colleagues for their valuable contribution to the ongoing debate on diagnostic precision of various *in vitro* and *in vivo* tests in the diagnosis of penicillin allergy. Our opinion is in line with theirs, namely that the precision of the tests applied should be evaluated against a gold standard, that is, oral or intravenous challenge with the culprit drug (except, of course, in cases of for example TEN, Stevens–Johnsons syndrome, DRESS, AGEP, or vasculitis, but including anaphylaxis). This strategy has, however, not been included in the present international guidelines.

For safety reasons, we have chosen a research strategy addressing the different steps in the diagnosis of penicillin allergy separately, that is, first to look upon the value of case history and the validity of the challenge procedures. These data are presented in our paper (1). Currently we are assess-

ing the value of skin testing in our patients and are finalizing a case series of oral challenge of patients with positive immediate intracutaneous test to penicillin(s), which will be followed by a protocol looking at oral challenge of patients with positive IgE to penicillin(s).

Conflicts of interest

None declared.

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Basophil activation test (BAT) in the diagnosis of immediate hypersensitivity reactions to radiocontrast media

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The article by Salas et al. (1) showed that the basophil activation test (BAT) was positive in 62.5% of cases confirmed as having hypersensitivity, showing a good correlation with the skin prick test (ST) and drug provocation test (DPT). However, this correlation appears to be poorly related to an immediate hypersensitivity reaction (IHR). The optimistic conclusions reported by the authors were echoed by other reports, where hypersensitivity to iodinated radiologic contrast media was evaluated to occur in 1–3% of patients and the possibility of shortening the diagnostic workup with BATs was announced as the main advantage of this test (2). Contrast material is generally well tolerated although approximately 1% of patients who receive low-osmolar non-ionic contrast material will develop anaphylaxis symptoms. Because most anaphylactic reactions are mild and nonallergic, clinically mimicking immunoglobulin E (IgE)-mediated allergy, diagnostic allergy testing has been discussed contro-

versially in the past and many contradictory comments have been raised (3, 4). Salas et al., used a BASOTEST™ method for their purposes; therefore, they captured basophils as anti-IgE-PE^{bright} cells and counted them for membrane CD63-FITC expression, a marker frequently used to evaluate basophil activation (5). A great individual variability in basophil response to contrast media by CD63 membrane upregulation has been recently reported (6). The induction of histamine and CD63 membrane upregulation by contrast media depends on the many pre-analytical factors such as temperature, extracellular calcium concentration, and IL-3 caused by handling and pre-analytical manoeuvres (6); these factors were not addressed in the article by Salas et al. (1). The use of iomeprol, as well as iopromide, has been associated also with a delayed-type non-IgE-mediated allergic hypersensitivity to the RCM (7). In the article by Salas et al., the highest BAT response was observed when RCM

contained iomeprol; furthermore, the RCM with unknown composition resulted in a significant correlation between ST and BAT only with iomeprol, much less with iodixanol and absent with iohexol (Table 1, Ref. 1). Subjects reacting to iomeprol do not exclude the hypothesis of a delayed response to RCM. Iomeprol, iodixanol, and iohexol share some organic group, principally a tri-iodo-phenyl-acetamide, which may exert a non-IgE-mediated cross-reaction; cross-reactivity was confirmed also by the authors (1). As emerging from the rate of IHR diagnosed in the discussed paper, BAT has not proved to be a valuable tool for an optimal

diagnostic evaluation in this occurrence, asking for some issues to be further addressed.

Conflict of interest

The author states that he has no conflict of interest.

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REPLY

We agree with Dr. Chirumbolo that radiocontrast media (RCM) administration is generally well tolerated as has been previously published. Also, we agree that most anaphylactic reactions are nonallergic in nature, and in fact this was an important conclusion of our study ('fewer than 10% of cases evaluated after having an immediate reaction due to RCM administration were finally confirmed as having hypersensitivity'). All of these facts were stated in Salas et al.'s article (1), so probably Dr. Chirumbolo has misunderstood this part.

Of all patients evaluated ($n = 90$), eight patients (8.9%) with anaphylaxis or immediate urticaria were clearly confirmed as having an immediate hypersensitivity reaction: five (62.5%) by skin tests and three (37.5%) by drug provocation tests. Since these eight patients were those with more severe reactions and the use of an *in vivo* diagnostic method may imply some risk, we and others (2) consider it important to use *in vitro* diagnosis, BAT being the most appropriate approach. In study, 62.5% of these eight patients were BAT positive, with controls being negative. Moreover, there was a good correlation with *in vivo* tests regarding the positive response to RCM administration. Therefore, it is difficult to understand why Dr. Chirumbolo stated that correlation appears poorly related to an immediate hypersensitivity reaction.

Regarding the technical issues, it is well known that a great individual variability in basophil response exists including spontaneous activation, therefore it was not considered necessary to comment on it in the text. To avoid this

variability, data were normalized and the result expressed as stimulation index (SI) as previously described in Torres et al. (3). Considering IL-3 as one of the factors that may influence BAT (4), it was included in the stimulation buffer (0.002 µg/ml) with no increase in healthy negative controls.

Iomeprol and iodixanol are the RCM most frequently involved in immediate and delayed-type hypersensitivity reactions (5, 6). These reactions are usually maculopapular exanthema or delayed urticaria, the diagnosis being based on either delayed reading intradermal/patch testing or drug provocation tests (5, 6). The clinical symptoms of delayed-type reactions as well as the diagnostic approach can clearly differentiate delayed-type reactions from the immediate. Therefore, it is difficult to confuse both types of reactions, especially considering that in our study those finally confirmed as immediate were clear anaphylaxis or immediate urticaria appearing in less than 1 h after RCM administration.

Conflict of interest

None declared.

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