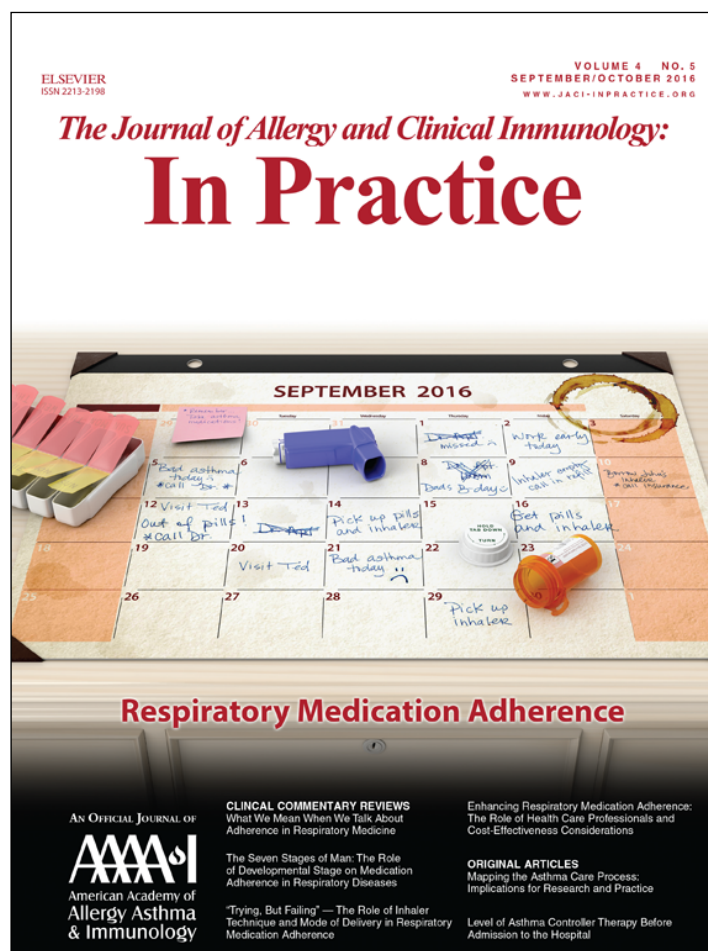




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plausibility as well as other criteria is not enough for establishing causality. Complementary tests including skin tests and *in vitro* tests as well as drug provocation test (DPT) are needed to establish or exclude the diagnosis.³ The quantification of the risk of DHR by the medical history can allow an estimate of the probability of having a DHR, but it does not allow estimating the risk of having a reaction during DPT. In this sense, patients having DHR after the administration of betalactam antibiotics or nonsteroidal anti-inflammatory drugs (NSAIDs) need to be challenged to establish cross-reactivity and achieve a precise diagnosis.^{4,5} Moreover, many other factors besides clinical history must be taken into account, such as infrastructure, time, or patient education.⁶

Another factor that can affect the calculations made by the mathematical models is differences between populations. In the present study, NSAIDs are the most frequently involved in DHR and betalactams antibiotics are the most frequently confirmed as allergic. In a recent study published by our group, in which we evaluated the largest series of DHR to date in terms of the number of patients and period evaluation, NSAIDs were the group of drugs most frequently involved in reactions reported by patients, representing almost 50% of the total, according to patient descriptions as well as those finally diagnosed according to DPT. In the case of betalactam antibiotics, however, more than 90% of patients had good tolerance after completing the evaluation.⁷ These data supported those published by another group and in a different population.³ In the present study, only 13 patients confirmed as cross-intolerance and 18 as selective responders to NSAIDs were included, and we think these data do not reflect the reality of other populations in whom NSAIDs represent the most frequent cause of confirmed DHR. Moreover, the number of patients with suspected reactions induced by NSAIDs is 114, which represents 46.7% of the total. We think that is a very high percentage of patients and a confirmed diagnosis is needed to develop a predictive model, not only suspected diagnosis.

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REFERENCES

1. Hierro B, Mateos J, Cabero MT, Mirón JA, Armentia A. A predictive model for the diagnosis of allergic drug reactions according to the medical history. *J Allergy Clin Immunol Pract* 2016;4:292-300.
2. Rubio M, Bousquet PJ, Gomes E, Romano A, Demoly P. Results of drug hypersensitivity evaluations in a large group of children and adults. *Clin Exp Allergy* 2012; 42:123-30.
3. Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med* 2004;140:1001-6.
4. Doña I, Blanca-López N, Cornejo-García JA, Torres MJ, Laguna JJ, Fernández J, et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. *Clin Exp Allergy* 2011;41:86-95.
5. Torres MJ, Blanca M. The complex clinical picture of beta-lactam hypersensitivity: penicillins, cephalosporins, monobactams, carbapenems, and clavams. *Med Clin North Am* 2010;94:805-20.

6. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003;58:854-63.
7. Doña I, Blanca-López N, Torres MJ, García-Campos J, García-Núñez I, Gómez F, et al. Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. *J Investig Allergol Clin Immunol* 2012; 22:363-71.

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Reply

To the Editor:

We have read with interest the letter by Moreno et al,¹ which takes issue with the methodology and findings of our article: "A predictive model for the diagnosis of allergic drug reactions according to the medical history."² We are, of course, aware of the good work carried out in this field by this group and have therefore considered our answer carefully. We have also read the letter by Doña et al,³ another group for which we have the greatest respect, about our article.

We stand by our results, and would like to emphasize that the objective of our study was a first attempt to generate a predictive model that could aid physicians in decision making. Likewise, although prospective studies would, undoubtedly, be the criterion standard for the construction of such models in general, our model was constructed explicitly on the information available in the medical history, as stated in our article; therefore, a retrospective design was not inappropriate.

Furthermore, our article explicitly states that age, for example, was routinely included in the analyses as is often the case, and that the number of drugs involved was also included for reasons that are explained. We also state in the article that IgE median 60 and emergency department visits, for example, were excluded as nonsignificant to show the simplest and most useful model. In fact, we state very clearly how the a priori probability of a patient having an adverse drug reaction (ADR) or not was calculated, and this took into account factors such as the drug class, because we agree that the probability of an ADR differs between drug classes.

Likewise, we did indeed state that 626 active principles were included: this was meant to mean that this number was the sum of all the active principles administered in all patients. If this is not clear, we apologize.

The intention of our work was to determine which set of variables was most predictive of an ADR or not. In this sense, the final model selected was that which best predicted the clinical diagnosis.

As explicitly stated in the article, our model was constructed according to the information available in the medical history, a common strategy used for many diseases. In general, we agree that prospective designs with *ad hoc* data registration are desirable. In fact, our article explicitly states that the use of mathematical models has limitations and that the use of models alone will never be sufficient. We are now preparing a further article that will present the promising results of the validation of the model, which has been carried out in a sample of nearly 1000 patients.

Undoubtedly, the addition of further variables would help refine and improve the model, but we repeat that our aim was to develop a simple, easy-to-use, and useful predictive model as an aid (among others) to assist in the diagnosis/ruling out of possible ADRs. Because of the current financial situation in Spain (and other countries), achieving an accurate diagnosis using the full



range of techniques currently available may take a considerable period of time and, in fact, many patients may not be diagnosed for years. In this situation, we believe that the further refinement of a simple-to-use tool for general practitioners or others could help to shorten this process and, perhaps, help to solve possible problems of overdiagnosis, with the costs this implies.

We thank our colleagues for their contribution to the scientific debate.

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REFERENCES

1. Moreno E, Muñoz-Bellido FJ, Laffond E, Dávila JJ. Predictive models in drug allergy: an appropriate patient selection is needed. *J Allergy Clin Immunol Pract* 2016;4:1015.
2. Hierro Santurino B, Mateos Conde J, Cabero Morán MT, Mirón Canelo JA, Armentia Medina A. A predictive model for the diagnosis of allergic drug reactions according to the medical history. *J Allergy Clin Immunol Pract* 2016;4:292-300.
3. Doña I, Salas M, Torres MJ. Mathematical models are not sufficient for the diagnosis of drug allergy. *J Allergy Clin Immunol Pract* 2016;4:1015-6.

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Diagnostic criteria for common variable immunodeficiency disorders



To the Editor:

We refer to the recent review of common variable immunodeficiency disorders (CVIDs)¹ written by experts in the field. Although the primary focus of the article was an overview of these disorders, the authors described new consensus diagnostic criteria for CVID (CVID ICON 2015). Differences between CVID ICON 2015 and our (Ameratunga et al 2013)² diagnostic criteria were presented in Table 2 of the article. Our criteria were not discussed in detail because of space constraints. We feel it is important to briefly describe our CVID diagnostic criteria and to highlight differences from the CVID ICON 2105 criteria.

Our criteria for CVID diagnosis have been previously described in depth and the reader is referred to these publications.² These articles contain the table of diagnostic categories and the algorithm for subcutaneous/intravenous immunoglobulin (SCIG/IVIG) treatment with supporting references.³ Briefly, the Ameratunga et al 2013 criteria comprise 4 categories: symptoms, signs, laboratory findings, and characteristic histology. There are no clinical or laboratory features that are pathognomonic for CVID. It is therefore essential that these categories are applied sequentially as each confers increasing specificity for the diagnosis.

To meet a diagnosis of probable CVID, patients must first fulfill all major category A criteria (age > 4 years, no secondary cause identified, and an IgG < 5 g/L for adults, based on the French

DEFI study). Patients must be symptomatic from their immune system failure (category B), which includes sequelae from increased susceptibility to infections, autoimmunity, and inflammatory disorders. Hypogammaglobulinemic patients who are completely clinically well do not qualify as having probable CVID, but may need to be treated with SCIG/IVIG, if they have markedly reduced IgG levels.⁴ Patients must also have at least 3 laboratory findings in category C, including reduction in IgA and/or IgM, reduction in memory B cells/increased CD21-low B cells, impaired or short-lived vaccine responses, serological evidence of significant autoimmunity, reduced IgG3 levels, absent isohemagglutinins, or sequence variations of genes predisposing to CVID. None of these findings are completely specific for CVID, and it is very important that they are interpreted in the context of symptomatic primary hypogammaglobulinemia (patients already fulfilling category A and B criteria).

Alternatively, patients with symptomatic primary hypogammaglobulinemia (meeting category A and B criteria) can qualify as having probable CVID if they have relatively specific histological lesions (category D), including absent plasma cells on biopsies, nodular lymphoid hyperplasia of the gut, nodular regenerative hyperplasia of the liver (NRH), or a sarcoid-like granulomatous disorder. We have shown that the histological features of CVID in the Ameratunga et al 2013 criteria can be useful in distinguishing patients with secondary immunodeficiencies as well as rare patients with a combined primary and secondary immune defect. The presence of these relatively specific histological markers (category D) may obviate the need to discontinue immunoglobulin treatment in a patient where the diagnosis is uncertain. A rectal biopsy may show the absence of plasma cells. We acknowledge that these histological lesions can occur in other conditions and must be interpreted in the context of symptomatic primary hypogammaglobulinemia (category A and B). NRH of the liver can, for example, occur with azathioprine treatment, but CVID would be excluded by dint of the patient not meeting category A criteria, as there is a secondary cause for the NRH.

We have also retained the possible and probable categories for CVID diagnosis, based on symptomatic state, as there may be changes in clinical and laboratory manifestations over time. In our view, a definitive diagnosis of CVID will only be established once the genetic basis of these disorders is understood. SCIG/IVIG treatment is primarily driven by evidence of immune system failure. Some patients with hypogammaglobulinemia may remain well once other predisposing factors for infections such as chronic tonsillitis are treated. These patients require close monitoring. Patients with mild hypogammaglobulinemia (IgG > 5 g/L) are deemed to have hypogammaglobulinemia of uncertain significance (HGUS). Some of these patients may evolve into CVID and require long-term follow-up. Some symptomatic patients with HGUS, particularly with bronchiectasis, will qualify for SCIG/IVIG treatment. When making decisions about SCIG/IVIG treatment, clinical judgment is paramount in the Ameratunga et al 2013 criteria.

Although it is an important component of CVID, impaired vaccine responses are given less prominence in the Ameratunga et al 2013 criteria. We have described in detail why vaccination responses can be difficult to measure and to interpret in patients with CVID.³ Patients with CVID who have had their primary vaccination series before antibody failure may be able to mount a protective response from long-lived memory B cells. We have