

G. CIPRANDI¹, P. COMITE², F. FERRERO², R. MONTARULI², M. MUSSAP²

Prescriptive appropriateness using inhalant and food allergen panels: a comparison between General Practitioners' and Allergists' prescription in Genoa (Italy)

¹Internal Medicine Department, ²Laboratory Medicine, IRCCS-AOU San Martino - IST, Genoa, Italy

KEY WORDS

allergen-specific IgE; panels; serum; appropriateness; prescription; specialist; general practitioner

Corresponding author

Giorgio Ciprandi
Largo R. Benzi 10
16132 Genoa
E-mail: gio.cip@libero.it

Summary

Background. Prescriptive appropriateness is an actual claim in healthcare, and it also concerns *in vitro* tests used in the allergy work-up, such as the serum allergen-specific IgE (sIgE) assay. In the Liguria Region, two panels were defined (for inhaled and food allergens) including 12 allergens. Their composition changed over time. **Objectives.** The aims of the present retrospective study were: i) to evaluate the percentage of positive tests, and ii) to compare the findings of sIgE assay on the basis of the general practitioners' (GPs) or specialist' prescription, considering both the old panels and the new panels. **Methods.** This retrospective study considered a population of adult patients, which consisted of 2368 subjects (68% females; mean age 50 years; age range: 10-103 years). Serum sIgE were measured by ImmunoCap system. **Results.** The percentages of positive tests were very low for food allergens and low for inhaled ones (ranging between 5% to 35%). There was change of prevalent prescriber with new panels. **Conclusions.** This study underlines the relevance of prescriptive appropriateness in the allergy work-up. The sIgE assay should be limited to those allergens that have a clinical relevance, based on clinical history.

Introduction

Allergic disorders have an impressive prevalence: up to 40% of the general population (1,2). Sensitization is the signature of the impaired immune response to allergen(s) in allergic patients, such as the on-going production of allergen-specific IgE. Sensitization is the condition necessary (but not sufficient) for diagnosing allergy. In fact, allergy is formally documented when symptoms appear after exposure to sensitizing allergen, otherwise sensitization has no clinical relevance. Thus, a sensitization has to be always interpreted during the allergy work up. Sensitization can be demonstrated *in vivo* (by skin prick test, SPT) or *in vitro* (by serum allergen-specific-IgE (sIgE) assay): the last is usually more precise, and well-defined serum IgE cut-offs have been associated with likely allergy diagnosis and clinical severity (3,4,5). On the other hand, serum sIgE assay is expensive, and the interpretation needs specific knowledge, mainly concern-

ing molecular components (6,7). In this regard, the convenience of using laboratory resource is extremely timely and indispensable. For a long time, the need of defining the prescriptive appropriateness in laboratory utilization has been acknowledged an impellent requirement. So, a long time ago van Walraven and Naylor performed a systematic review of published studies, that measured inappropriate laboratory use and methodological criteria, including implicit and explicit ones (8). They concluded that many studies confirmed an inappropriate use of laboratory tests. This issue is always more mandatory in light of narrowed health-care budget and the global concept of appropriateness of care is up-to-date (9). In this context, it is necessary that the prescription of lab test is based on appropriateness criteria.

On the basis of this premise, the Italian Health Ministry issued a decree (DM 9 December 2015) that defined the "conditions of dispensation and prescriptive appropriateness indications for a series of health services for outpatients, including tests for al-

lergy diagnosis, namely skin prick test and sIgE assay. Thus, SPT was defined first level test in the allergy work up and should be prescribed only by the specialist. However, sIgE assay should be prescribed as second level, such as confirmatory test, when SPT cannot be carried out or is not thorough, also it may be prescribed only by the specialist. As expected, this decree has raised many objections, mainly by General Practitioners (GPs) and family paediatricians who felt a limitation of their professional autonomy. Therefore, the Ministry defined a series of indications for its application at the end of March 2016. This document states that the application is presently on an experimental stage, so both GPs and family paediatricians may prescribe a basic test, consisting of no more than 12 allergen-specific IgE.

On the other hand, the Liguria Region some years ago defined two panels of 12 allergen-specific IgE (for inhaled or food allergens) that could be prescribed by both GPs and specialists. Later, the composition of both panels was revised, including some molecular components.

On the basis of these considerations, the aims of the present retrospective study were: i) to evaluate the percentage of positive tests, and ii) to compare the findings of sIgE assay on the basis of the GPs or specialist prescription, considering both the old panels and the new panels.

Materials and methods

Patients

This retrospective study considered a population of adult patients, which consisted of 2368 subjects (68% females; mean age 50 years; age range: 10-103 years). The patients were sent by GPs or specialists to the Laboratory Medicine Service of the University-Hospital San Martino of Genoa (Italy) for serologic assessment, as they suffered from complaints suggestive for respiratory and/or food allergy.

The old panels were in effect from January 2007 to May 2014. The new panels have been introduced in the clinical practice since June 2014.

The old inhaled panel included: *Dermatophagoides pteronyssinus* (D1), *Dermatophagoides farinae* (D2), *Cynodon dactylon* (G2), *Lolium perennis* (G5), *Alternaria alternata* (M6), birch (T3), hazelnut tree (T4), olive tree (T9), *Parietaria officinalis* (W19), dog (E5), and *Ambrosia trifida* (W3). The old food panel included: egg white (F1), milk (F2), fish (F3), wheat (F4), shrimp (F24), tomato (F25), egg yolk (F75), α -Lactalbumin (F76), casein (F78), and hazelnut (F17).

The new inhaled panel includes: *Artemisia absinthium* (W5), *Parietaria officinalis* (W19), *Cupressus sempervirens* (T23), olive tree (T9), cat (E1), dog (E5), *Alternaria alternata* (M6), *Dermatophagoides pteronyssinus* (D1), Bet v 1 (T215), Bet v 2 (T216), Pru

p 3 (F420), *Phleum pratense* (G6). The new food panel includes: milk (F2), fish (F3), wheat (F4), peanut (F17), soybean (F14), hazelnut (F17), shrimp (F24), egg white (F1), Pru p 1 (F419), Pru p 3 (F420), Pru p 4 (F421), and Bet v 2 (T216).

All patients gave the written informed consent, and the Review Board of the IRCCS-AOU San Martino-IST approved the procedure.

Assay

Serum levels of specific IgE were detected by the IFMA procedure (ImmunoCAP, Thermo Fisher Scientific, Uppsala, Sweden) in peripheral blood samples from patients. Serum was collected into gel-separator tubes, centrifuged and stored at -20 °C until analysis. Measurement of circulating specific IgE antibodies was performed according to manufacturer's instructions (10). Specific IgE concentrations were expressed in kUA/L according to the traceable calibration to the 2nd IRP WHO for Human IgE, and 0.35 kUA/L has been considered as a cut-off for defining positivity, such as sensitization (11).

Analytical quality control was performed both by using an internal quality control (Immunocap Specific IgE Control LMH, Thermo Scientific, Uppsala, Sweden) and by participating to an external quality assessment scheme (UK NEQAS, Herries Road Sheffield).

Statistical analysis

Numbers were analysed by χ^2 test. A p-value < 0.05 was considered as statistically significant. Data were analyzed using Stata statistical package version 13.1 (StataCorp, College Station, TX, USA).

Results

Old panels

Inhaled allergens: the test was performed in 847 patients. The panel was requested more frequently by GPs (96%) than by specialists (4%). **Figure 1** reports the percentages of positivity for the single allergens considering the prescription by GPs or specialists. There were significant differences between GPs' and specialists' prescriptions, such as positive results were more common for specialists' prescriptions, for hazelnut tree ($p < 0.0001$), olive tree ($p < 0.0001$), *Parietaria officinalis* ($p < 0.0001$), dog ($p < 0.0001$), and *Ambrosia trifida* ($p = 0.04$).

Food allergens: the test was performed in 1187 patients. The panel was requested more frequently by GPs (99%) than by specialists (1%). **Figure 2** reports the percentages of positivity for the single allergens considering the prescription by GPs or specialists. There was no significant difference between GPs' and specialists' prescriptions for all tested allergens.

Figure 1 - New and old panels for inhaled allergens, considering the prescription made by the GP or the specialist.

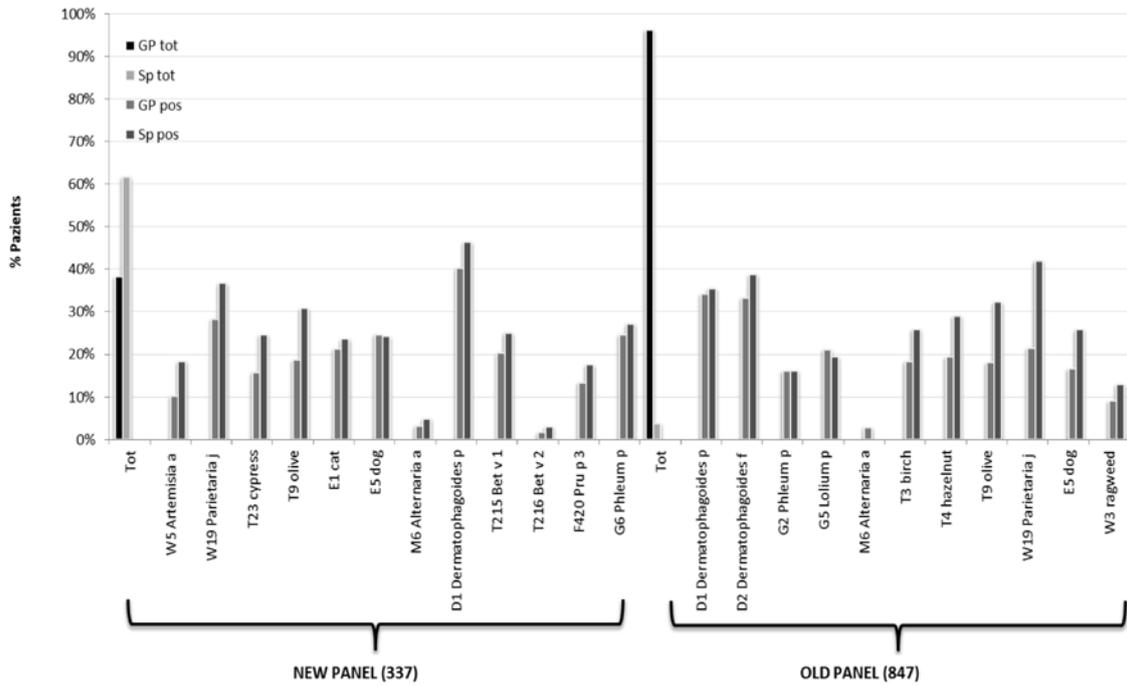
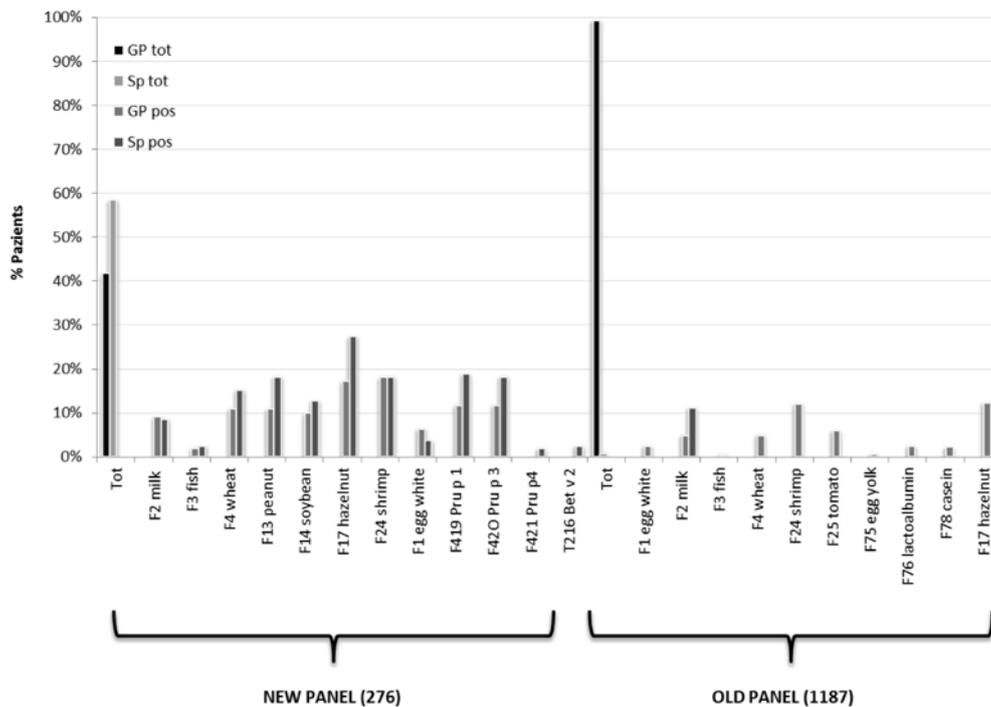


Figure 2 - New and old panels for food allergens, considering the prescription made by the GP or the specialist.



New panels

Inhaled allergens: the test was performed in 337 patients. The panel was requested more frequently by specialists (62%) than by GPs (38%). **Figure 1** reports the percentages of positivity for the single allergens considering the prescription by GPs or specialists. There was significant difference between GPs' and specialists' prescription, such as positive results were more common for specialists' prescriptions, for Pru p 3 ($p = 0.0006$) alone.

Food allergens: the test was performed in 276 patients. The panel was requested more frequently by specialists (60%) compared with GPs (40%). **Figure 2** reports the percentages of positivity for the single allergens considering the prescription by GPs or specialists. There was no significant difference between GPs' and specialists' prescriptions for all tested allergens.

Discussion

sIgE is usually envisaged as the main biomarker for the allergic phenotype, as allergic disorders are paradigmatically characterized by an IgE-mediated inflammation. IgE measuring is a common way to work up allergy.

The present study aimed to investigate the percentage of positive tests and the comparison of the findings considering the GPs' or specialists' prescription, both for the old panels and the new panels defined by the Liguria Region.

The study was conducted on a large cohort of subjects referring to serologic assessment for suspected respiratory or food allergy. Firstly, this study demonstrated that there was a relevant difference between the number of prescriptions by GPs or specialists: the ratio between GPs' and specialists' prescriptions was initially disproportionate in favor of GPs, but then it inverted using the new panels. The percentages of positive tests were very low for food allergens, mainly for old panels, and low for inhaled allergens. These findings denote a scarce appropriateness in using predefined panels. In this regard, it is noteworthy to consider the reimbursement price: € 71.18 for extract allergens (up to 12 allergens) and € 9.92 for each molecular component. On the other hand, the productive cost ranges between € 12 and 15. So the use of panels is in and of itself unprofitable, but considering the present outcomes it seems inappropriate. In fact, an efficacy of 10-30% of panels does not justify their prescription. This consideration agrees with a recent document provided by Italian society of allergy, asthma and clinical immunology (SIAAIC) that reported a list of identified 5 most inappropriate allergological procedures (12). More recently, a document has been published to improve the appropriateness in the field of respiratory allergy suggesting a direct interaction between allergists and policy makers / institutions (13).

Anyway, the current study had some limitations: it was retrospectively conducted on a selected patient population sample, subjects referring for serologic assessment, there was no fol-

low-up, and there are no clinical data. This issue is particularly relevant, as sensitization does not always correspond to allergy: this fact probably further reduces the percentages of subjects really "positive" to tests, such as allergic. In addition, this study did not consider possible confounding factors, such as smoking status, parasite infestation, environmental exposures, seasonal variations, and number of co-sensitizing allergens. Therefore, there is need to conduct cohort studies and long-term follow up trials to confirm these preliminary findings. However, the strength of the present study is represented by the large size of the sample: higher than in the other studies.

In conclusion, this study underlines the relevance of prescriptive appropriateness in the allergy work-up. The sIgE assay should be limited to those allergens that are clinically relevant.

References

1. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA). 2008 Update (in collaboration with the World Health Organization, GA2LEN and AllerGen). *Allergy*. 2008;63(Suppl. 86):8-160.
2. WAO White book on allergy. www.worldallergy.org
3. Comite P, Ferrero F, Mussap M, Ciprandi G. Par j 2 IgE measurement for distinguishing between sensitization and allergy. *Allergol Int*. 2015;64:384-5.
4. Ciprandi G, Comite P, Ferrero F, Bignardi D, Minale P, Voltolini S, et al. Birch allergy and oral allergy syndrome: The practical relevance of serum immunoglobulin E to Bet v 1. *Allergy Asthma Proc*. 2016;37:43-9.
5. Platts-Mills TAE, Schuyler AJ, Erwin EA, Commins SP, Woodfolk JA. IgE in the diagnosis and treatment of allergic disease. *J Allergy Clin Immunol*. 2016;137:1662-70.
6. Sastre J. Molecular diagnosis in allergy. *Clin Exp Allergy*. 2010;40:1442-60.
7. Matricardi PM, Kleine-Tebbe J. Molecular allergology between precision medicine and the choosing wisely initiative. *Clin Exp Allergy*. 2016;46:664-7.
8. van Wairaven C, Naylor CD. Do we know what inappropriate laboratory utilization is? *JAMA*. 1998;280:550-8.
9. Brook RH. Assessing the appropriateness of care - its time has come. *JAMA*. 2009;302:997-8.
10. Leimgruber A, Mosimann B, Claeys M, Seppey M, Jaccard Y, Aubert V, Peitrequin R, Nisoli MP, Pécoud A. Clinical evaluation of a new in-vitro assay for specific IgE, the immuno CAP system. *Clin Exp Allergy*. 1991;21:127-31.
11. Seagroatt V & Anderson SG. The second international reference preparation for human serum immunoglobulin E and the first British standard for human serum immunoglobulin E. *Journal of Biological Standardization*. 1981;9:431-7.
12. Heffler E, Landi M, Quadri S, Incorvaia C, Pizzimenti S, Vernero S, et al. Choosing wisely in Allergology: a slow medicine approach to the discipline promoted by the Italian society of allergy, asthma and clinical immunology (SIAAIC). *Clin Mol Allergy*. 2015;13:28.
13. Lombardi C, Savi E, Costantino MT, Heffler E, Milanese M, Passallacqua G, et al. Appropriateness in allergic respiratory diseases health care in Italy: definitions and organizational aspects. *Clin Mol Allergy*. 2016;14:5.