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Do mucosal biomarkers reveal the immunological state associated with food allergy?

To the Editor,

As food allergy is an immunological disorder that affects mucosal surfaces, the search for biomarkers may be promising for reflecting an implication of the mucosal immune system. The purpose of this letter was to report the ability of the mucosal biomarkers to identify food allergy patients. A systematic review (SR) was undertaken to evaluate the mucosal biomarkers associated with food allergy. Search strategies in the LILACS, LIVIVO, PubMed, Science Direct, Scopus, and Web of Science databases included the following terms: (allergy OR allergies OR allergic OR allergen OR allergenic OR "food allergy" OR "food allergies") AND (food OR egg OR milk OR peanut OR dairy OR nut) AND (salivary OR "saliva" OR "Saliva"[Mesh] OR nasal OR lacrimal OR gut OR fecal OR "oral fluid") AND ("Biomarkers"[Mesh] OR biomarker OR "biomarkers" OR "biological marker" OR "biological markers" OR marker OR markers OR biomolecule OR biomolecules OR IgA OR IgE OR "secretory antibodies"). The search databases and methods are detailed in Figure S1.

Twenty-two studies met the eligibility criteria and were included in this SR. The sample size was composed of 1950 subjects (1220 food allergy cases and 730 controls). Sixteen different biomarkers

were assessed (Figure 1). Eosinophil cationic protein (ECP) was the most commonly reported biomarker (nine studies), followed by fecal calprotectin and IgA/IgG (six studies) and by IgE and α 1-antitrypsin (AAT) in four studies. Eosinophil protein X, tumor necrosis factor- α (TNF α), and tryptase were reported in three studies. Other biomarkers were reported twice or once such as eosinophil-derived neurotoxin (EDN), histamine, human β -defensin 2 (HBD2), metabolites, B-cell-activating factor (BAFF), 5-hydroxytryptamine, myeloperoxidase (MPO), prostaglandin D2 (PGD2), and peroxidase. (Table S1). Eighteen studies reported biomarkers that may be useful for diagnosis or treatment follow-up. A higher concentration of gut/fecal or salivary biomarkers in allergic patients or after challenge test than healthy controls or negative challenge was reported. All studies reported that the double-blind, placebo-controlled food challenge (DBPCFC) was done for diagnosis purposes. However, only few studies detailed if a challenge test was carried out before or after the collection of sample.

Four studies did not show differences in biomarker levels between patients and controls. Fecal and gut lavage fluid was the most frequently studied samples, whereas only two studies analyzed

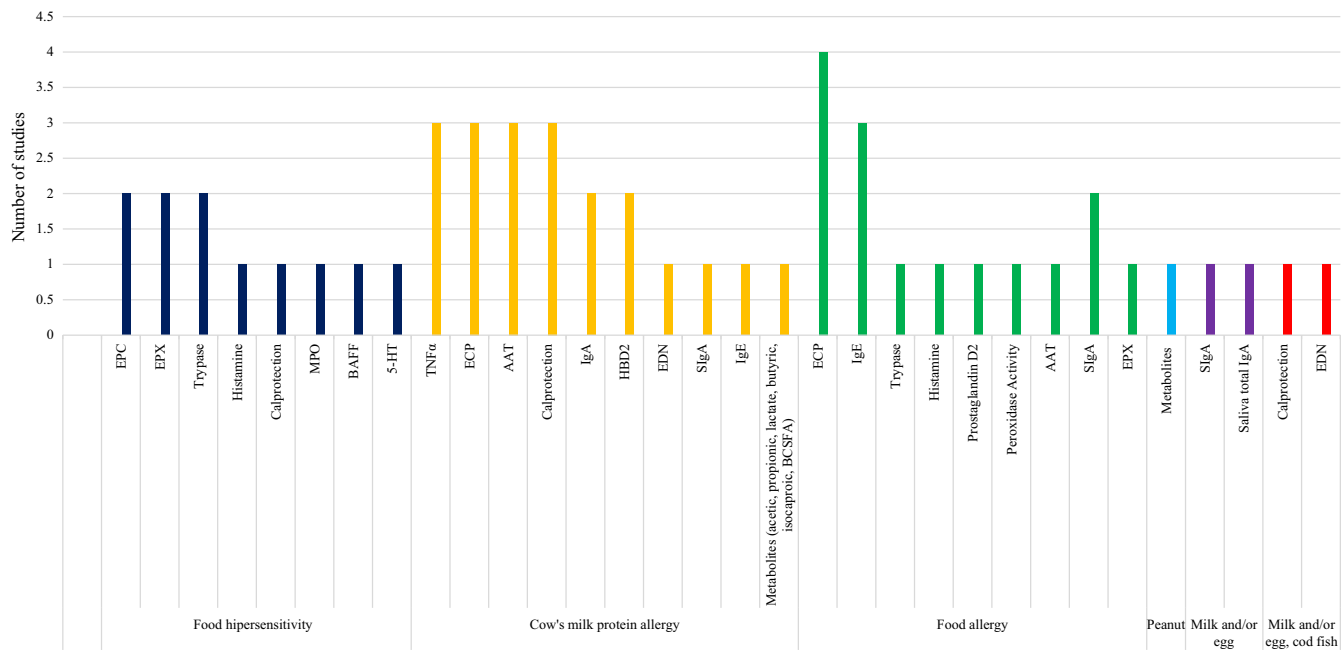


FIGURE 1 Biomarkers analyzed in the studies included in the systematic review organized by the type of food allergy or hypersensitivity. 5-HT, 5-Hidroxitriptamina; AAT, α 1-antitrypsin; BAFF, B cell-activating factor; BC SFA, Branched-chain short fatty acids; ECP, Eosinophil Cationic Protein; EDN, Eosinophil-Derived Neurotoxin; EPX, Eosinophil Protein X; HBD2, Human β -defensin2; IgE, Immunoglobulin E; MPO, Myeloperoxidase; SlgA, Secretory Immunoglobulin A; TNF α , Tumor necrosis factor- α [Colour figure can be viewed at wileyonlinelibrary.com]

saliva samples. Additionally, the most frequent type of food allergy was cow's milk allergy, reported in eight studies.

This SR showed that despite the large and increasing number of studies concerning biomarkers for food allergy, there is clearly no consensus regarding which biomarkers possess the best diagnostic value, which molecules constitute the most accurate type of biomarker (ie, proteins, nucleic acids, or metabolites), or which is the best detection method to use. Several biomarkers (mostly from gut/fecal samples) were proposed, but only five were reported more than three times and revealed the inflammatory state of the gut (ECP, Calprotectin, AAT) rather than the immunological disorder associated with allergy (IgA, IgE).

Inflammatory biomarkers such as ECP and calprotectin are considered as putative biomarkers for food allergy. ECP plays a role in diverse biological mechanisms such as RNase, cytotoxic, and immunoregulatory functions.^{1,2} This functional heterogeneity appears to be related to genetic variations of the *ECP* gene. Recently, the report of polymorphisms of *ECP* gene of patients with Crohn's disease and ulcerative colitis suggests an essential role of eosinophils in the pathophysiology of inflammatory bowel disease (IBD).³ Calprotectin is a calcium-binding protein (S100A8/S100A9 oligomer), secreted mainly by neutrophils, and having antimicrobial properties.⁴ Fecal calprotectin is considered a reliable marker of intestinal inflammation with good clinical sensitivity. It is used in the differential diagnosis of IBD, as well as in its follow-up and treatment management.^{5,6}

Considering IgE as the gold standard of the immunological biomarkers associated with allergy, the presence of total IgEs in gut/fecal samples was variously reported in different studies. One study

showed no differences between patients and controls, whereas three others estimated that the level of gut/fecal IgE was increased in case of allergy. This discrepancy may be explained firstly by the fact that some types of food allergy are not IgE-mediated, and the distinction among IgE-mediated and non-IgE-mediated forms was not always clearly indicated (Table S1). Secondly, as the IgEs are not secretory immunoglobulins, the presence of IgEs in gut/fecal samples comes from a blood exudate that reveals the inflammatory state of the mucosa. Thus, the presence of IgE in gut/fecal samples may be considered as an indirect marker of gut inflammation, whereas its presence in serum reveals the immunological disorder. Indeed, the "hygiene hypothesis"⁷ suggests that the IgE-mediated reactions may be associated with an imbalance in the immune response regulation that would result from a decrease to the normal exposure to environmental microbial antigens. Thus, subject to a rich and diverse microbial environment, the mucosal immune system would be rather tolerogenic, and a mucosal stimulation deficit could be associated with an abnormal IgE production inducing an inflammatory response.

Surprisingly, only very few data are available concerning the status of the mucosal immune system in cases of allergy, even if the allergic process affects mostly mucosal surfaces such as gut and oral mucosae for food allergy and nasal and ocular mucosae for airborne allergens. The present review shows that for food allergy, the results concerning the production of secretory IgA are sparse, sometimes without comparison with healthy people, and evaluating total rather than specific IgA. However, several studies show an inverse relationship between the production of secretory IgA and the development of respiratory allergies, suggesting that IgAs play a protective role in the development of allergic asthma.⁸ Thus, further studies are

needed to investigate the diagnostic/prognostic value of allergen-specific secretory IgAs in food allergic patients. Until now, gut/fecal samples were preferred to saliva for the characterization of food allergy biomarkers probably because food allergies are considered only as gastrointestinal disorders. However, if we consider that food allergies may be associated with a dysregulation of the mucosal immune system (eg, breaking of oral tolerance), the quantification of allergen-specific secretory IgA may be done on salivary samples, as the saliva-based clinical testing may be a safe, noninvasive, and low-cost method for diagnosis.⁹

In conclusion, this SR demonstrates that gut/fecal biomarkers emerge as potentially promising in the diagnosis of food allergy. The most frequent was ECP, calprotectin, IgA, and IgE. Further research is required for the following purposes (a) to validate these biomarkers in a well-structured, population-based prospective cohort study without convenience samples; (b) to compare the prognostic value of inflammatory biomarkers (mostly ECP and calprotectin) in various situations of gut inflammatory reactions; and (c) to evaluate the efficiency of the mucosal immune system of patients with food allergy compared to healthy population or other nonallergic pathologies of the gut. Therefore, further research concerning the mucosal immune response to food allergens is necessary in order to understand the underlying immunological disorder and thus provides a personalized treatment.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure 1 (online supplement). Flow Diagram of literature search and selection criteria adapted from PRISMA

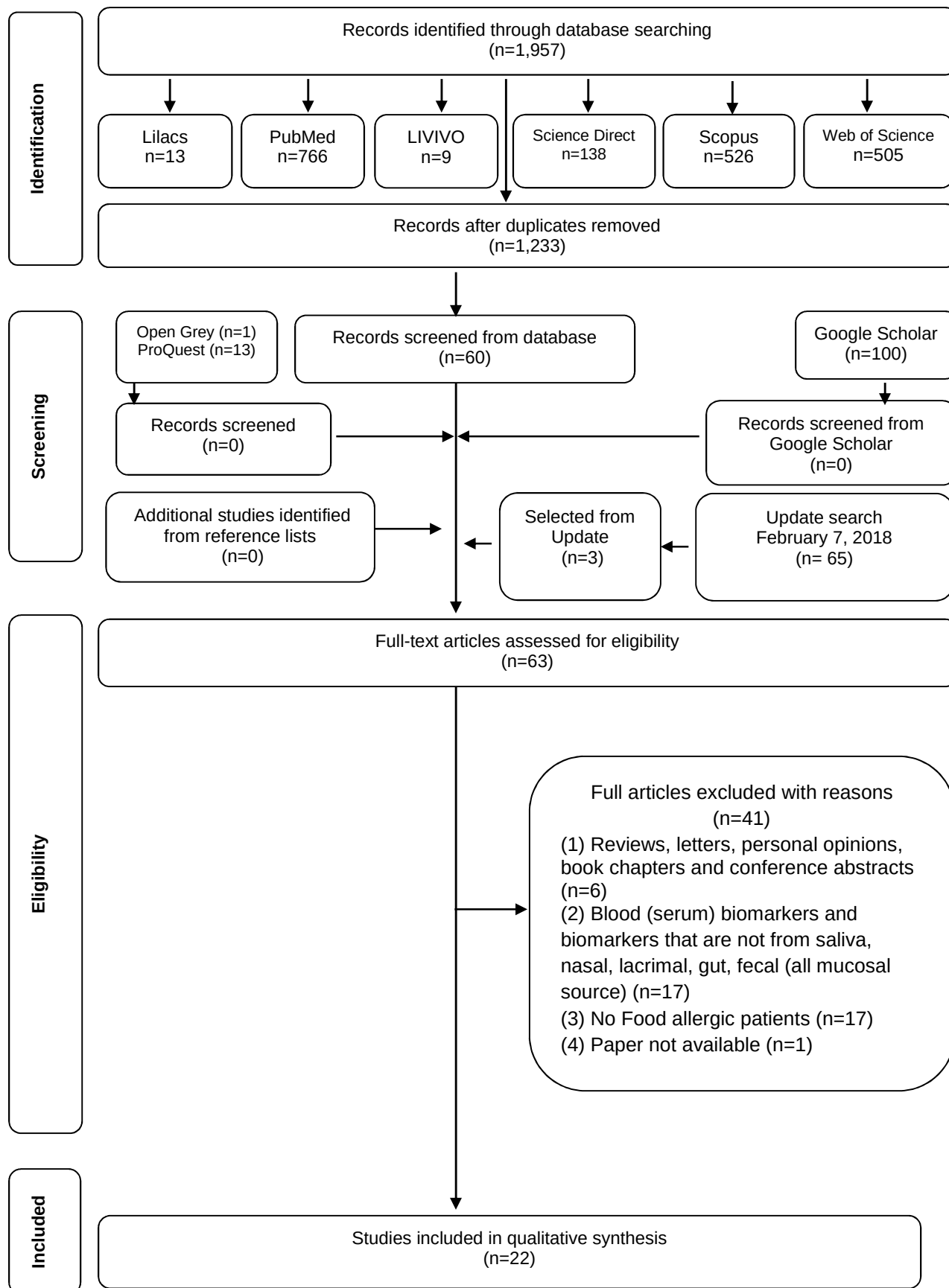


Table 1 (online supplement). Summary of descriptive characteristics of included studies (22 studies)

Type of Food Allergy	Author, Year, Country	Cases of food allergy (N° of IgE mediated)	Controls	Age (years/ months)	Methods	Biomarkers	Sample Origen
Food hypersensitivity	Arslan et al., 2004, Norway	52 (21 IgE mediated)	44 non-atopic individuals	K= 19–80 years (mean 39) C= 19–83 years (mean 38)	Histamine (HR-Test); ECP and tryptase (Unicap FEIA system); Calprotectin (ELISA and PhiCal® test)	Histamine; ECP; Tryptase; Calprotectin	Gut lavage fluid and Fecal samples
	Gregersen et al, 2011, Norway	69 (non-IgE mediated)	35 healthy volunteers; 27 with inflammatory bowel disease	K= 21–83 years (mean 39) C= 23–61 years (mean 33)	Liquid chromatography tandem mass spectrometry (Agilent 1100 series LC/MSD)	5-hydroxytryptamine (5-HT, serotonin)	Gut lavage fluid
	Lied et al, 2010, Norway	60 (40 IgE mediated)	20 controls	K= 20–73 years (mean 41) C= 24–44 years (mean 32)	ELISA	BAFF	Gut lavage fluid
	Magnusson et al, 2003, Sweden	13 (3 IgE mediated)	No controls	K= 26–68 years (mean 52)	Radioimmunoassays (RIA)	ECP; EPX; MPO	Fecal samples
	Van Odijk et al, 2006, Sweden	11 (4 IgE mediated)	4 controls	K= 28–70 years (mean 44) C= 34–49 years (mean 38)	ImunoCAP RIA	Tryptase; EPX	Fecal samples
Cow's milk protein allergy (CMPA)	Belizón et al. 2016, Spain	82 (non-IgE mediated)	30 controls	K= 1-12 months C= 1-12 months	Electrochemi-luminescence immunoassay (ECLIA); fluorescent enzyme immunoassay (FEIA); Bacterial stool culture and latex agglutination tests; ELISA	Calprotectin	Fecal samples
	Beşer et al., 2014, Turkey	32 (24 IgE mediated; 8 non-IgE mediated)	39 controls	K= 12.5±8.58 months C= 11.5±7.6 months	ELISA	Calprotectin	Fecal samples

Food allergy	Kalach et al, 2013, France	25 (3 IgE mediated)	No controls	K= 1-18 months (mean 6.3)	Immunonephelometric method adapted on the BN ProSpec. System, ELISA, real-time qPCR	AAT; TNF α ; Calprotectin; HBD2; Total sIgA; EDN	Fecal samples
	Kapel et al, 1999, France	13 (NR)	10 controls	K= 17 $\pm$ 15 months C= 20 $\pm$ 9 months	Immunoenzymometric assay kit, CAP system	TNF α ; Total IgE; ECP	Fecal samples
	Majamaa et al, 1996, Finland	71 (NR)	No controls	K= 3-60 months (median 14)	ELISA	TNF α ; AAT; ECP	Fecal samples
	Merras-Salmio et al, 2014, Finland	57 (non-IgE mediated)	22 controls	K= 0-4 years (median 8.7 months)	ELISA	HBD2; Total sIgA; Calprotectin	Fecal samples
	Saarinен et al, 2002, Finland	102 (65 IgE mediated 37 non-IgE mediated)	106 controls	K= 7 months C= 7 months	CAP system ELISA Single radial immunodiffusion	AAT; ECP; Total sIgA	Fecal samples
	Thompson-Chagoyan et al, 2011, United Kingdom	46 (46 IgE mediated)	46 controls	K= 2-12 months C= 2-12 months	gas-liquid chromatography	Metabolites: Acetic; propionic; lactate; butyric; isocaproic; BCSFA	Fecal samples
	Andre et al., 1995, France	312 (NR)	95 controls	K= 1-74 years (mean 30) C= 1-76 years (mean 32)	Radioimmunologic method	Total IgE	Fecal samples
	Hua et al., 2017 Taiwan	83 (83 IgE mediated)	189 infants without IgE sensitization	K and C= 6-12 months	Immunoassay system	Total sIgA; ECP	Fecal samples
	Majamaa et al, 1999, Finland	25 (NR)	13 controls	K= 0.4–1.3 years (mean 0.6) C= ND	Fluoroimmunoassay and RIA	EPX; ECP	Fecal samples

	Santos et al, 1999, Spain	8 (8 IgE mediated)	7 controls	K= 20-26 years C= 20-26 years	RIA Enzyme Immunnoassay Enzymatic Kinetics Turbidimetry	Tryptase; Histamine; Prostaglandin D ₂ ; ECP; Peroxidase Activity	Intestinal Lavage fluid
	Sasai et al, 1992, Japan	11 (11 IgE mediated)	5 controls	K=5 months to 2 years C= 5 months to 1 year	Time resolved Fluoro-immunometric DELFIA Enzyme immunoassay nephelometric immunoassay	AAT; Total IgE; Total sIgA	Fecal samples
	Schwab et al, 2001, Germany	11 (11 IgE mediated)	20 controls	K= 25-61 years C= 17-78 years	CAP system RIA	Total IgE; ECP	Intestinal lavage fluid
Peanut	Peeters et al, 2011, The Netherlands	12 (NR)	11 controls	K= 18-33 years (mean 25.4) C= 21-57 years (mean 27.3)	Nuclear magnetic resonance (NMR) spectroscopy	Metabolites	Saliva
Milk and/or egg	Tomicic et al, 2009, Sweden	89 (NR)	No controls	K=below 2 years of age	ELISA	Total sIgA; Total IgA	Saliva
Milk and/or egg, Cod fish	Winberg et al, 2016, Sweden	20 (NR)	7 controls	K=11-12 years C=11-12 years	ELISA	Calprotectin; EDN	Fecal samples

Legend: K=Case. C=Control. Histamine release Test=HR-Test. Fluorescence enzyme immunoassay=FEIA. Quantitative Polymerase Chain Reaction=qPCR. Reverse transcription–polymerase chain reaction analysis=RT-PCR. Enzyme-linked immune-sorbent assay=ELISA. Matrix-assisted laser-desorption/ ionization – mass spectrometry=MALDI_MS. Liquid chromatography -tandem mass spectrometry =LC-MS/MS. Multiplex ligation-dependent probe amplification=MLPA. Surface enhanced laser desorption/ ionization=SELDI-MS. Methylation-specific polymerase chain reaction=MSP. Ultra-performance Liquid Chromatography–Mass Spectrometry=UPLC–MS. H Nuclear Magnetic Resonance Spectrometry=NMR. Radioimmunoassay=RIA. Eosinophil Cationic Protein=ECP. Eosinophil Protein X=EPX. Myeloperoxidase=MPO. B cell-activating factor=BAFF. α 1-antitrypsin=AAT. Tumor necrosis factor- α =TNF α . Human β -defensin2=HBD2. Secretory ImmunoglobulinA=sIgA. Immunoglobulin E=IgE. Eosinophil-Derived Neurotoxin=EDN. Elevated chromogranin A serum=serum CgA. Gastrointestinal inflammatory=GI. Fecal calprotectin=FCP. Electrochemiluminescence immunoassay=ECLIA. Cow’s milk protein allergy=CMPPA. Branched-chain short fatty acids=BCSFA. Double-blind, placebo-controlled food challenge =DBPCFC. NR= Not

reported, indicates the papers in which the authors did not classify the IgE-mediated and non IgE mediated forms, even if allergen specific-IgEs were quantified in some papers.

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