Cow's Milk Allergy: the Relevance of IgE

Maria Angela Tosca,¹ Angela Pistorio,² Giovanni Arturo Rossi,¹ Giorgio Ciprandi^{3*}

¹Pulmonary Disease and Allergy Unit, Istituto Giannina Gaslini, Genoa, Italy

²Epidemiology and Biostatistics Service, Istituto Giannina Gaslini, Genoa, Italy

³Medicine Department, IRCCS - Azienda Ospedaliera Universitaria San Martino, Genoa, Italy

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Cow's milk allergy (CMA) accounts for most diagnosed food allergies, mainly in the first year of life.¹ CMA can cause severe anaphylaxis.² CMA management is based on strict avoidance and the prescription of rescue medication.

Cow's milk (CM) contains more than 40 proteins, including casein (Bos d 8), -lactalbumin (Bos d 4), and -lactoglobulin (Bos d 5), identified as major milk allergens.¹ Serum specific IgE (sIgE) to casein characterized patients with persistent CMA,³ CM tolerance,⁴ and reactivity to baked milk.⁵

Oral immunotherapy (OIT) for CMA has been used with interesting outcomes as it may induce immunologic tolerance.^{1,2} However, a safety perspective represents a relevant concern, because reactions to OIT are frequent.^{1,2} It has been demonstrated that sIgE to raw CM >50 kUA/L predicted not-tolerated OIT.⁶

Molecular-based allergy diagnostics have now become recently available in clinical practice. This method allows for defining and characterizing the sensitization profile that identifies potentially dangerous proteins and suggests a more precise prognosis. In this regard, Cingolani and colleagues reported that component resolved diagnosis had a good ability to define 2 phenotypes of CMA children: "high-anaphylaxis risk" and "milder-risk".⁷

In particular, these phenotypes can be differentiated through measuring the level of sIgE to Bos d 8. We now report our experience concerning a retrospective cohort. This observational and retrospective experience evaluated the usefulness of ImmunoCAP and ISAC (please describe company, city, country) to detect anaphylaxis after CM ingestion. We evaluated children with CMA diagnosis who consecutively visited the Istituto Gaslini (a third tier children's hospital) in the last year. CMA diagnosis was performed on suggestive history consistent with CM sensitization (*i.e.* symptom occurrence after milk ingestion), documented milk sensitization, and a positive food challenge test. Anaphylaxis was defined according to validated cri-

teria: briefly, suggestive history (sudden occurrence of symptoms, involving at least two systems, such as gastrointestinal and/or cutaneous and/or respiratory and/or cardiovascular after milk ingestion) consistent with documented CM sensitization.¹ Serum sIgE to: raw CM allergen, Bos d 4, 5, and 8 were measured by the quantitative ImmunoCAP method and the semi-quantitative microarray-ISAC method (Thermo Fisher Italy).

We Evaluated 53 patients (20 with anaphylaxis and 33 with CMA). Children with anaphylaxis presented: skin symptoms (89%), respiratory complaints (77%), gastrointestinal features (57%), and cardiovascular symptoms (11%). Children with CMA presented: skin symptoms (71%), gastrointestinal features (65%, mainly vomiting), and respiratory complaints (58%). The Table shows the clinical and immunologic characteristics of the 2 groups. The significant prevalence for male gender in anaphylaxis was consistent with that of Cingolani's study. The age was significantly lower in the anaphylaxis group, it conflicted with the findings of that study (surprisingly the age was particularly old in regards to CMA). Serum sIgE levels to raw CM allergen were significantly higher in the anaphylaxis group; however, there was no significant difference between the two groups for all molecular components as measured by both the ImmunoCAP and ISAC method.

Receiver operating characteristic (ROC) analysis showed that raw CM ImmunoCAP had a good specificity (86.7%), but weak sensitivity (52.9%), fair positive (69.2%), and negative (76.5%) predictive value, with Diagnostic Odds Ratio (OR_{Diagn}) 7.3. The

Correspondence to: Giorgio Ciprandi, MD, Viale Benedetto XV 6, 16132 Genoa, Italy.

Tel: +39-10-35338120; Fax: +39-10-3538664; E-mail: gio.cip@libero.it

Received: February 13, 2014; Revised: March 24, 2014;

Accepted: April 24, 2014

• Partially funded by Ricerca Corrente - Italian Ministry of Health.

• There are no financial or other issues that might lead to conflict of interest.

Table. Clinical and immunological characteristics of patients

	Anaphylaxis: yes	Anaphylaxis: no	<i>P</i> *	Cut-off [†]	AUC	Sens %	Spec %	OR _{Diag} (95% CI)
	Median (1st-3rd q)	Median (1st-3rd q)						
Number of patients	20	33						
Gender: male-n (%)	15 (75.0)	15 (45.4)	0.04					
Age (months)	5.5 (4.0-6.5)	32.4 (15.3-68.2)	<0.0001					
Total IgE (kU/L)	682 (165-1,439)	197 (106-459)	0.11					
Cow milk (kU _A /L)	39.6 (5.8-50.9)	4.7 (0.9-16.5)	0.02	>30.0	0.70	52.9	86.7	7.3 (1.8-30.2)
nBos d 4 (kU _A /L)	5.7 (0.5-32.1)	1.5 (0.7-3.5)	0.13	>12.2	0.65	42.9	95.2	15.0 (1.5-145.2)
nBos d 5 (kU _A /L)	7.5 (1.3-15.3)	1.3 (0.6-3.8)	0.07	>2.07	0.68	71.4	66.7	5.0 (1.1-21.8)
nBos d 8 (kU _A /L)	8.2 (3.4-53.0)	6.4 (1.4-17.6)	0.61	>36.6	0.56	36.4	83.3	2.9 (0.5-16.4)
nBos d 4 (ISU)	0.9 (0.1-3.7)	0.2 (0.2-1.0)	0.58					
nBos d 5 (ISU)	1.0 (0.1-5.4)	0.2 (0.2-0.6)	0.14					
nBos d 8 (ISU)	1.0 (0.1-4.1)	0.2 (0.2-0.5)	0.10					

*P values refer to the Mann-Whitney *U* test; [†]Cut-off values were determined by means of the receiver operating characteristic (ROC) curve analysis. Sens %, sensitivity; Spec %, specificity; OR_{Diag}, diagnostic odds ratio; 95% CI, 95% confidence interval; AUC, area under the ROC curve.

assessment of molecular components by ImmunoCAP was unsatisfactory in regards to area under the ROC curve (AUC), sensitivity, and specificity, despite the fair positive and negative values. The micro-assay ISAC method was also unreliable in our setting.

We believe that the diagnostic work-up for CMA should consider a molecular-based allergy diagnostic as well as a raw allergen assessment to obtain more useful information for the management and possible identification of risk factors.

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