The Egyptian Journal of Hospital Medicine (April 2021) Vol. 83, Page 838-843

Assessment of CoMiSS among Children with Cow's Milk Allergy at Zagazig University Hospital

Azza Ibrahim El Desouky, Heba Gamal Anany, Ibrahim Sobhy Ibrahim Mohammed
Department of Pediatrics, Faculty of Medicine, Zagazig University, Zagazig, Egypt
***Corresponding Author: Ibrahim Sobhy Ibrahim Mohammed, Mobile: (+20)** 01020237797**,**
Email: dr.Ibrahim1986@gmail.com

ABSTRACT

Background: Cow's milk protein allergy (CMPA): The topic of definition still causes confusion among physicians. Words such as "allergy," "intolerance," and "hypersensitivity" are used interchangeably. The accepted definition of allergy is "a hypersensitivity reaction triggered by specific immunologic mechanisms". There is no such thing as "allergy to lactose" but rather lactose intolerance. The authors introduced the acronym "CoMiSS" (cow's milk-related symptom score). **Objective:** To evaluate CoMiSS in children with cow's milk allergy at Pediatric Department, Faculty of Medicine, Zagazig University. **Patients and Methods:** This study was conducted during the period from December 2018 to May 2020. Cow's milk-related symptom score was assessed.
Results: There was statistically significant increase in eosinophilic count among confirmed CMA than no CMA. There was statistically significant higher total score of CoMiSS among confirmed CMA than no CMA, and another one regarding each symptom of CoMiSS score. Accuracy of CoMiSS in diagnosis of CMA was 90.8%. The percentage was for sensitivity (86.4%), specificity (93.4%), positive predictive value (88.3%) when the score is >12 and negative predictive value (92.2%). **Conclusion:** CoMiSS is a simple, fast, and easy-to-use tool to raise awareness and help in early diagnosis of CMPA, but hard to handle with many of illiterate mothers. CoMiSS is a helpful tool and applicable method to screen for CMPA, though there may be risk of under-diagnosis when CoMiSS≥12 is used as the criterion for early pick-up of CMPA in Egyptian infants.
Keywords: Assessment-CoMiSS, Cow's milk allergy in children.

INTRODUCTION

Cow's milk protein allergy (CMPA): The topic of definition still causes confusion among physicians. Words such as "allergy," "intolerance," and "hypersensitivity" are used interchangeably. The accepted definition of allergy is "a hypersensitivity reaction triggered by specific immunologic mechanisms". There is no such thing as "allergy to lactose" but rather lactose intolerance [(1)]. A food allergy is "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food". Cow's milk protein allergy (CMPA), which is also commonly referred to as cow's milk allergy (CMPA), is the leading cause of food allergy in infants and children younger than three years [(2)].

Cow's milk (CM) protein allergy (CMPA) is an immune reaction to specific CM proteins occurring in 2–5% of infants, presenting with skin, gastrointestinal (GI) and/or respiratory symptoms [(3)]. CMPA is a reproducible adverse reaction of an immunological nature induced by cow's milk proteins [(4)].

The authors[(5)] introduced the acronym "CoMiSS" (cow's milk-related symptom score awareness tool). The score was assessed in symptomatic infants (aged two weeks to six months) at initial diagnosis of CMPA, and later when placed on the CMFD. Oral food challenge (OFC) was positive in 80% of infants in which CoMiSS decreased to ≤6 after one month of elimination diet [(5)]. Since then, four other reports confirmed the high predictive value of CoMiSS in relation to the CM OFC; the reduction of the score to <6 was also associated with the response to CMFD [(6)].

Recently, an international study tested the score in a population of healthy infants and found a median value of 3 [(7)]. The Cow's Milk-related Symptom Score was developed to increase awareness of mainly non-IgE mediated CMPA [(8)].

The recommended diagnostic approach for CMPA relies on a 2 to 4 week elimination diet followed by an oral food challenge (OFC). While the double-blind, placebo-controlled food challenge (DBPCFC) is the gold standard for the diagnosis of food allergy, in clinical practice open challenges are generally considered sufficient, particularly in infants and young children [(9)].

Parents are often reluctant to proceed with a food challenge as CMPA symptoms may recur during a positive OFC [(10)]. Primary care physicians are the first to encounter cases of CMPA. Inadequate awareness among of CMPA can predominantly attributed to the lack of guidelines and unswerving diagnostic methods. Hence, there is a dire need for a tool such as Cow's Milk-related Symptom Score (CoMiSS) that brings about awareness to help recognize CMPA in infants [(8)].

The study aimed to assess the value of Cow's milk related symptoms score (CoMiSS) in the prediction of cow's milk allergy in pediatrics.

Received:10 /8 /2020
Accepted:29 /8/2020

PATIENTS AND METHODS

This study was conducted during the period from December 2018 to May 2020 at Pediatric Department, Faculty of Medicine, Zagazig University. This study was interventional one which included 120 infants (aged up to 18 month) presenting with one or more of the following CMPA symptoms: cutaneous (atopic dermatitis and urticaria), respiratory (cough and dyspnea, rhinitis), and gastrointestinal (digestive regurgitation, vomiting, rectal bleeding, constipation and diarrhea).

Ethical approval:

This study was ethically approved from Institutional Reviewer Board (IRB) in Faculty of Medicine, Zagazig University and a parental consent from every case caregiver that participates in this research was taken.

Target population: Infants up to 18 months of age at the time of enrolment who had signs and symptoms of cow's milk allergy

Sample size: Assuming that the target population in Pediatrics Department of Zagazig University Hospital is about 5 cases per week so at six months about 120 cases of suspected Cow's milk allergy. All of cases was taken as comprehensive sample.

Inclusion criteria: Male or female infants aged up to 18 months. Infants suffered from CMPA symptoms.

Type of the study: Interventional study

All infants were subjected to the following:

A- Full history taking (age and sex) and type of feeding.

B- Full clinical examinations with emphasis on assessment of weight and height, chest, skin and abdominal examination.

C- Investigations:

- Complete blood count (CBC) was done using Sysmex KX-21N **(11).**
- Stool analysis (pH, reducing substance, WBC, Occult blood, Parasites).
- Serum albumin was measured using human ELISA (sandwich technique) kits provided **(11).**

A predesigned questionnaire, with informed consent obtained from parent/primary caregiver of the infant, was used to collect information pertaining to the general characteristics and anthropometry, medical and feeding history and clinical examination via CoMiSS **(7).**

- Crying was only considered if the child was crying for 1 week or more, assessed by the parents, without any other obvious cause
- Reading the Result: The scoring ranges from 0 to 33. Each symptom has a maximal score of 6, except respiratory symptoms where the maximal score is 3.
- If final score > 12, the symptoms are likely cow's milk related. This could potentially be CMPA.
- If final score < 12, the symptoms are less likely related to cow's milk. Look for other causes.
- CMPA diagnosis can only be confirmed by an elimination diet followed by an oral food challenge.

Bristol Stool Chart (12).

The type of stool or feces depends on the time it spends in the colon. Feces is basically the result of diet, fluids, medications and lifestyle. Of each one the Bristol Stool Chart checks what stools are telling.

The Bristol Stool Chart shows seven categories of stool. Every person will have different bowel habits, but the important thing is that stools are soft and easy to pass – like types 3 and 4 below.

- Type 1-2 indicate constipation
- Type 3-4 are ideal stools as they are easier to pass, and
- Type 5-7 may indicate diarrhea and urgency.

Skin: An easy to apply score based on an estimation of the surface covered by the dermatitis, using the surface estimation drawings from burns**.**

Respiratory: Respiratory symptoms are considered in the CoMiSS although they have been given less importance (lower weighting) because most of the time chronic cough, runny nose and even wheezing are caused by viral infections. However, respiratory symptoms can be caused by cow's milk.

D- Food Challenge Test:

A drop of the formula is put on the lips. If no reaction occurs after 15 min, the formula is given orally and the dose is increased stepwise (0.5, 1.0, 3.0, 10, 30, 50 to 100 ml) every 30 min. The infant was observed for an additional 2 h in the hospital after the last dose was administered, while being monitored for any reaction. Acute reactions were defined as those occurring within 2 h of the last dose of CM during the challenge. In the absence of an acute reaction, the parents were instructed to give the infant at least 250 mL per day of a standard CM-protein based formula starting the following morning for 14 days.

During this period we continued to monitor symptoms, including gastrointestinal, cutaneous, respiratory or general. Delayed reactions were considered up to 2 weeks from the OFC. A positive OFC was considered when at least one of the following symptoms occurred: Urticaria (>3 hives), severe lip or face edema, generalized erythema, persistent sneezing or rhinorrhea or dry cough, hoarseness, wheezing or stridor, at least two episodes of vomiting or loose stools, altered mental status/hypo reactivity or cardiovascular collapse **(13).**

Interpretation:

Positive challenge: CMPA confirmed:

If symptoms of CMPA re-appear, the suspected diagnosis of CMPA is confirmed and the infant should be maintained on an elimination diet using extensively hydrolyzed formula (EHF) and amino acid formula (AAF) until the child is between 9 and 12 months of age, but for at least 6 months, whichever occurs first. The challenge is then repeated. If it is possible to follow the infant with IgE mediated allergy with Skin prick tests (SPTs) and/or specific IgE determination, normalization or improvement of these tests would help in choosing the time point of challenge. Supplementary feeding should be introduced carefully to avoid accidental intake of CMP. Nutritional counselling must ensure a sufficient intake of the therapeutic formula (eHF or AAF) to guarantee adequate calcium intake.

Negative challenge: no CMPA: Children who do not develop symptoms on the cow's milk formula during challenge and up to 1 week after follow-up can resume their normal diet, although they should be monitored. Clinicians should advise parents to be attentive for delayed reactions, which may evolve over several days following the challenge.

Statistical analysis

The data were coded, entered and processed on computer using Statistical package for the social sciences (SPSS) (version24). Mean, standard deviation, frequency, and percentage were used as descriptive statistics. The following tests were used: Chi-Square test (X^2), independent student's t-test, and receiver operator characteristic curve. The accepted level of significance in this work was stated at 0.05.

RESULTS

This study showed that: The mean of the age (6.60 ± 4.82), weight (Kg) (6.37±1.79), birth weight (3.14 ± 0.34), and the percentage of female (55%) and male (45%). This study showed that the mean of the total score of CoMiSS was (11.2 ± 2.8).

This table (1) shows that the percentage of the <12 was 64.2% of and >12 was 35.8%.

Table (1): Categories of total CoMiSS first visit

		No.	%
Code	**<12**	77	64.2
	>12	43	35.8

The results of OFC test are shown in table 2.

Table (2): OFC Test at ≥ 2 Weeks Elimination

Immediate Reactions (up to 2hrs after CMP ingestion)		
Symptoms	Mild to Moderate	Severe
No. of patients	11	2
Delayed Reactions (after 2 - 72hrs after CMP ingestion)		
Symptoms	Mild to Moderate	Severe
No. of patients	26	5

There was statistically significant difference between confirmed CMA and no CMA regarding type of feeding and early complementary food (Table 3).

Table (3): Comparison between confirmed CMA (positive challenge test) and no CMA (negative challenge test) regarding type off and complementary food

			Confirmed CMA (positive challenge test) (No.= 44)	No CMA (negative challenge test) (No.= 76)	P. value
Type of Feeding	**Breast F**	**No.**	5	20	<0.001
		%	11.4%	26.3%	
	Fresh Cow milk	**No.**	7	2	
		%	15.9%	2.6%	
	Formula F	**No.**	21	13	
		%	47.7%	17.2%	
	Mixed F	**No.**	11	41	
		%	25%	53.9%	
Early complementary food (dairy products)	**No**	**No.**	17	51	<0.003
		%	38.6%	67.1%	
	Yes	**No.**	27	25	
		%	61.4%	32.9%	

There was statistically significant difference between confirmed CMA and no CMA regarding family history of allergic diseases (Table 4).

Table (4): Comparison between Confirmed CMA (positive challenge test) and no CMA (negative challenge test) regarding Family history of allergic diseases

			Confirmed CMA (positive challenge test) (No.= 44)	No CMA (negative challenge test) (No.= 76)	P. value
Family history of allergic diseases	-ve	No.	7	52	<0.001
		%	15.9%	68.4%	
	+ve	No.	37	24	
		%	84.1%	31.6%	

There was statistically significant difference between confirmed CMA and no CMA regarding stool (Table 5).

Table (5): Comparison between confirmed CMA (positive challenge test) and no CMA (negative challenge test) regarding stool

			Confirmed CMA (positive challenge test) (No.= 44)	No CMA (negative challenge test) (No.= 76)	P. value
Stool	Soft stool	No.	0	24	<0.001
		%	.0%	31.6%	
	Normal stool	No.	0	0	
		%	.0%	.0%	
	Hard stool or liquid stool	No.	30	49	
		%	68.2%	64.5%	
	Watery stool	No.	14	3	
		%	31.8%	3.9%	

There was no statistically significant difference between confirmed CMA and no CMA regarding skin (Table 6).

Table (6): Comparison between confirmed CMA (positive challenge test) and no CMA (negative challenge test) regarding skin

			Confirmed CMA (positive challenge test) (No.= 44)	No CMA (negative challenge test) (No.= 76)	P. value
Skin	Absent	No.	20	32	0.747
		%	45.4%	42.1%	
	Mild	No.	10	21	
		%	22.7%	27.6%	
	Moderate	No.	9	18	
		%	20.5%	23.7%	
	Severe	No.	5	5	
		%	11.4%	6.6%	

There was statistically significant increase in total score of CoMiSS among confirmed CMA than no CMA (Table 7).

Table (7): Comparison between confirmed CMA (positive challenge test) and no CMA (negative challenge test) regarding total CoMiSS

		Confirmed CMA (positive challenge test) (No.= 44)	No CMA (negative challenge test) (No.= 76)	P. value
Total score of CoMiSS	**Mean ± SD**	11.2 ± 2.82	5.3 ± 3.359	.000

Accuracy of CoMiSS in diagnosis of CMA was 90.8%, the percentage was for sensitivity (86.4%), specificity (93.4%), positive predictive value (88.3%) when the score is >12 and negative predictive value (92.2%) (Table 8).

Table (8): Accuracy of CoMiSS in diagnosis of CMA

Total CoMiSS	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %	Accuracy %
cut off value 12	86.4%	93.4%	88.3%	92.2%	90.8%

DISCUSSION

In the current study, regarding clinical manifestations among confirmed CMPA cases, (86.3%) had occult bloody in stools, (31.8%) with watery stool, (54.6%) with skin manifestations, and (40.9%) with respiratory symptoms. This comes in accordance with **Zeng *et al.*** [6] who found that, regarding clinical manifestations among 24 affected infants definitely diagnosed with CMPA, there were 18 infants (75%) with eczema, 15 infants (62.5%) with bloody stools, 15 infants (62.5%) with diarrhea, 5 infants (20.8%) with regurgitation, and 3 infants (12.5%) with slow weight gain, 2 infants (8.3%) with repeated cough and asthma and 1 infant (4.2%) with crying. There was immediate reaction in 4 infants with rashes and delayed reaction in 20 infants during OFC in confirmed CMPA group. **Domínguez-Ortega *et al.*** [14] demonstrated that, the majority of affected children had one or more symptoms involving one or more organ systems, mainly the gastrointestinal tract and/or skin.

This study showed that, there were statistically significant increase in eosinophilic count among confirmed CMA than no CMA. This result was supported by **El-Sebay *et al.*** [15]. Their study was carried out on 70 participants classified into group 1: it included 50 infants with cow milk protein allergy and group 2: it included 20 age and sex-matched apparently healthy participants. They found that, there was a significant increase in eosinophil % in group 1 when compared with group 2.

In our study, there was statistically significant lower albumin among confirmed CMA than no CMA. This is in harmony with **Altinel Acoglu *et al.*** [16] who found that hypoalbuminemia was associated with CMA.

Our study showed that, there were statistically significant higher total score of CoMiSS among confirmed CMA than no CMA, and another one regarding each symptom of COMISS score. These results agreed with **Prasad *et al.*** [4] who found that, the mean CoMiSS of the children was 16.2 ± 6.8. The minimum CoMiSS was 2, and the maximum was 32. A score of above 12 was seen in 72% (60 of 83) of the children, warranting further evaluation and need for confirmatory diagnosis of CMPA. Overall, 84.3% (70 of 83) of the children were diagnosed with CMPA via oral food challenge/ImmunoCAP test. Fifty-five out of seventy of the confirmed cases of CMPA showed a CoMiSS > 12 while five out of thirteen cases did not show a confirmed diagnosis of CMPA even with CoMiSS > 12. This primarily suggested CoMiSS to be a particularly useful tool in diagnosing CMPA. This is in harmony with a study by **Zeng *et al.*** [6] who aimed to evaluate the effect of CoMiSS in early identification of CMPA in Chinese infants. They calculated CoMiSS for 38 infants with suspected CMPA diagnosed in the pediatric gastroenterologic clinic in their hospital. They found that the results of rank sum test showed that there was a significant difference in CoMiSS between two groups ($P < 0.05$).

This study showed that, accuracy of CoMiSS in diagnosis of CMA was 90.8%. The percentage was for sensitivity (86.4%), specificity (93.4%), positive predictive value (88.3%) when the score is >12 negative predictive value (92.2%). This result was supported by **Zeng *et al.*** [6] who revealed analysis of sensitivity and specificity of CoMiSS. ROC curve was with 87.5% sensitivity and 78.6% specificity.

These results agreed with **Salvatore *et al.*** [17] who aimed to assess the accuracy of the cow's milk-related symptom score (CoMiSS) in response to a cow's milk-free diet (CMFD). They prospectively recruited 47 infants (median age three months) who had been placed on a CMFD due to persisting unexplained gastrointestinal symptoms and compared data with 94 healthy controls. The CoMiSS score was completed at recruitment and while on the exclusion diet. In 19/47 (40%) cases a response to the diet occurred. They found that, the receiver operation characteristic (ROC) curve identified a CoMiSS score of 9 to be the best cut-off value (84% sensitivity, 85% specificity, 80% positive (PPV) and 88% negative predictive value (NPV)) for the response to CMFD. They found CoMiSS to be a useful tool to help identify infants with persisting

gastrointestinal symptoms and suspected CMA that would benefit from CMFD. Also, **Prasad *et al.* [4]** who reported CoMiSS had a positive predictive value (PPV) of 93%, negative predictive value (NPV) of 33%, with sensitivity of 77%, and specificity of 66%. A receiver operating characteristics (ROC) curve area of 0.68 at a CoMiSS cutoff of 12 was observed.

As **Vandenplas *et al.* [8]** said, CoMiSS is a simple score that will help clinicians to efficiently identify CMPA early, though it cannot be used as a diagnostic tool or a substitute for OFC test. The primary GI physician supervising the OFC is not absolutely blinded to the CoMiSS scores. It is easily to make the results to have bias. The application value of CoMiSS needs to be further confirmed by multi-center large sample studies. OFC is considered the gold standard method to diagnose CMA **[17].**

A CoMiSS > 12 was seen in 72% of the children; and overall, 84.3% of the children were diagnosed with CMPA via oral food challenge/ImmunoCAP test, which suggests that CoMiSS can be used as an easy and predictive tool in the diagnosis of CMPA [18]. Another studies conducted by **Vandenplas *et al.* [8, 19]** suggested that a low CoMiSS even after absence of cow's milk protein and its derivatives for one month can have a considerable risk of a positive challenge test (odds ratio, 0.83; 95% confidence interval, 0.75–0.93; p = 0.002). Although these data are not substantial enough to deduce an inference, the findings resonate that a CoMiSS>12 may be a vital cutoff value to recognize symptoms related to CMPA in infants. In addition, its ability to hint towards a diagnosis in less time, and its ease of use by general physicians, is a vital advantage of the tool. CoMiSS can be a vital step in delaying the progression of CMPA, help in its early diagnosis, and prevent misdiagnosis; in addition, it cuts down parental anxiousness as well. Early data show the predictive value of the tool in identifying infants at risk of CMPA of 80%. CoMiSS being an effortless tool is a practical method to help reduce the delays and difficulties associated with CMPA, thus reducing the ongoing stress among infants and parents as well as healthcare professionals.

CONCLUSION

CoMiSS is a simple, fast, and easy-to-use tool to raise awareness and help in early diagnosis of CMPA, but hard to handle with many of illiterate mothers. CoMiSS is a helpful tool and applicable method to screen for CMPA, though there may be risk of under-diagnosis when CoMiSS≥12 is used as the criterion for early pick-up of CMPA in Egyptian infants.

REFERENCES

1. **Boyce J, Assa'ad A, Burks A *et al.* (2010):** Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol., 126: 1–58.
2. **Sicherer S (2011):** Epidemiology of food allergy. J Allergy Clin Immunol., 127:594–602.
3. **Sicherer S, Sampson H (2018):** Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J. Allergy Clin Immunol., 141: 41–58.
4. **Prasad R, Venkata R, Ghokale P *et al.* (2018):** Cow's Milk-related Symptom Score as a predictive tool for cow's milk allergy in Indian children aged 0–24 months. Asia Pac Allergy, 8(4): 36-45.
5. **Vandenplas Y, Steenhout P (2014):** A pilot study on the application of a symptom-based score for the diagnosis of cow's milk protein allergy. SAGE Open Med., 13: 2-9.
6. **Zeng Y, Zhang J, Dong N (2019):** Assessment of Cow's milk-related symptom scores in early identification of cow's milk protein allergy in Chinese infants. BMC Pediatr., 19: 191-195.
7. **Vandenplas Y, Mukherjee R, Dupont C *et al.* (2018):** Protocol for the validation of sensitivity and specificity of the Cow's Milk-related Symptom Score (CoMiSS) against open food challenge in a single-blinded, prospective, multicenter trial in infants. doi:10.1136/bmjopen-2017-019968
8. **Vandenplas Y, Dupont C, Eigenmann P *et al.* (2015):** A workshop report on the development of the Cow's Milk-related symptom score awareness tool for young children. Acta Paediatr., 104:334–339.
9. **Koletzko S, Niggemann B, Arato A *et al.* (2012):** Diagnostic approach and management of cow's milk protein allergy in infants and children: a practical guideline of the GI- committee of ESPGHAN. J Pediatr Gastroenterol Nutr., 55: 221–9.
10. **Vandenplas Y, Steenhout P, Planoudis Y (2013):** Treating cow's milk protein allergy: a double-blind randomized trial comparing two extensively hydrolyzed formulas with probiotics. Acta Paediatr., 102:990–8.
11. **Shalaby N, Sayed R, Zhang Q *et al.* (2017):** Systematic discovery of genetic modulation by Jumonji histone demethylases in Drosophila. Scientific Reports, 7: 5240.
12. **Heaton K, Lewis S (1997):** Stool form scale as a useful guide to intestinal transit time. Scandinavian Journal of Gastroenterology, 32: 920 - 924.
13. **Sampson H, Gerth van Wijk R (2012):** Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol., 130: 1260–1274.
14. **Domínguez-Ortega G, Borrelli O, Meyer R *et al.* (2014)** Extraintestinal manifestations in children with gastrointestinal food allergy. J Pediatr Gastroenterol Nutr., 59(2):210–214.
15. **El-Sebay H, Badr E, El-Ghobashi Y *et al.* (2016):** The role of specific IgE antibodies in infants with cow milk protein allergy. Menoufia Med J., 29:874-80.
16. **Altinel Acoglu E, Akcaboy M, Melek Oguz M *et al.* (2016):** Hypoalbuminemia and Malnutrition Associated with Cow's Milk Allergy: A Case Report. Iranian Red Crescent Medical Journal, 18(6): 34810-15.
17. **Salvatore S, Bertoni E, Bogni F *et al.* (2019):** Testing the Cow's Milk-Related Symptom Score (CoMiSS™) for the Response to a Cow's Milk-Free Diet in Infants: A Prospective Study. Nutrients, 11(10): 2402-6.
18. **Vandenplas Y, Steenhout P, Järvi A *et al.* (2017):** Pooled analysis of the Cow's Milk-related-Symptom-Score (CoMiSS) as a predictor for cow's milk related symptoms. Pediatr Gastroenterol Hepatol Nutr., 20:22–6.
19. **Vazquez-Ortiz M, Ludman S, Aston A *et al.* (2019):** Lip dose challenges in food allergy: current practice and diagnostic utility in the United Kingdom. J Allergy Clin Immunol Pract., 7(8): 2770–2774.