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Specific oral tolerance induction (SOTI): adverse reactions and their treatments during both in hospital and home phase

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Introduction

Specific oral tolerance induction (SOTI) is a promising approach in the treatment of severe food allergy. Recent reports have demonstrated the efficacy of different oral desensitization protocols with limited side effects.[1-5] Nevertheless, the number of children who have undergone these protocols is still small and SOTI is considered an experimental approach to be limited to highly defined settings. Data regarding the incidence and severity of adverse reactions during hospital SOTI show a wide range varying from infrequent, mild reactions[6,7] to frequent, severe ones.[8] This was likely due to the variation in the patients' specific IgE levels or the variation in the increase of the cow's milk (CM) dose from patient to patient during the protocols. The available data on the follow-up of home phase SOTI refer to limited series, with low specific IgE levels and a short-term follow-up.[9-11]

SOTI has been applied at the Burlo Garofolo Hospital since January 2001. The rush phase was a hospital based SOTI, with an estimated 10 day hospitalization period. It was applied to children with a positive oral food challenge test for less than a single dose of 4 mL or with a history of recent, severe reactions occurring within the previous year and requiring emergency room care, and with high specific IgE levels (> 70 kUA/L). Once the patients were released, the protocol was continued at home.

AIMS

To define during both the in-hospital rush phase and home phase of SOTI, the incidence and severity of adverse reactions, the possible risk factors related to the patients and the protocol, and lastly, the safety and efficacy of nebulized epinephrine as a first-line treatment of respiratory reactions.

Materials and method

Consensus and ethical committee approval: Informed consent was obtained from all parents. The ethical committee of the IRCCS, Burlo Garofolo, Trieste, approved the study.

Definition of cases: Children who had a positive double blind placebo controlled food challenge (DBPCFC) or presented with an objective symptom during the course of hospital SOTI were included in the study. Children in this latter group were enrolled without DBPCFC for any of one or more of the following reasons: a positive open challenge, a history of recent severe reactions requiring emergency room care within the previous year, specific IgE level > 70 kUA/L, or refusal of the parents to allow the child to undergo a DBPCFC.

Method of evaluating the radioallergosorbent test (RAST) classes: The RAST was determined through the CAP system from Pharmacia and Upjohn AB Diagnostics, Uppsala, Sweden. The specific IgE levels were reported as both a mean number of RAST specific IgE levels (kUA/L) and as a median RAST class because the laboratory did not define the value > 100 kUA/L in the sixth class.

Evaluation of patients: Prior to beginning the hospital phase of SOTI, all patients underwent spirometry. In 2008, a nitric oxide test and a standard ECG were also included in the protocol in order to reveal possible hidden arrhythmias. During the course of a bronchospasm SOTI was delayed and in the case of poorly controlled asthma, a treatment with

nebulized steroids, nebulized beta-2 agonists or oral anti-leukotriene antagonists (according to the National Asthma and Prevention Program Guidelines[12]) was promptly begun. A 24 gauge cannula, inserted following the application of anesthetic cream, was kept in place during the entire hospitalization period and checked each day for patency.

In hospital CM administration protocol: The 10 days protocol for CM administration was developed based on small initial doses[7] (Table 1). The increase in CM was regulated according to the patient's symptoms and reactions. The increase was stopped whenever grade 4 reactions occurred and/or in the case of diffuse severe urticaria. The day after the grade 4 reactions, the corresponding daily doses were halved. In this way, the dose which provoked the initial reaction was re-introduced the following day. For example, a child who reacted on day 8 to 7 mL of CM would have received on day 9, 4 mL, 6 mL, and 8 mL, respectively. While on day 10, the first CM dose was begun at 7 mL. As a rule, the number and severity of reactions did not change the length of admission, but might have changed the amount of single CM dose reached at discharge (the more severe the reactions, the slower the increase and lower the dose of CM at discharge). Patients who did not experience any adverse symptoms during the first few days of SOTI were given increasing doses of CM until symptoms were provoked. In these cases, admission could last less than 10 days, and the patient was discharged with a higher tolerance of CM, resulting in a larger initial dose during the home phase.

Definition and treatment of adverse reactions during the hospital phase: Adverse reactions were classified according to the Clark scale[13] which was modified by introducing significant gastric pain as an additional reaction. This was defined as abdominal pain lasting more than 15 min, interfering with the child's activities, forcing the child to remain in bed, and associated with an increase in heart rate or pallor. Adverse reactions were treated according to EAACI (European Academy of Allergy and Clinical Immunology) guidelines[14]. However, nebulized epinephrine was introduced as a first-line treatment for respiratory reactions. Acute gastric pain was managed with oral beclomethasone (400 μg), while oral cromolyn (250 mg) was administered 30 min before each CM dose as prophylaxis for recurrent gastric pain episodes. EAACI guidelines were further modified by discouraging the use of oral or intravenous (IV) steroids unless strictly necessary, due to the possible masquerading effect on the reactions in the following days. Epinephrine was the only drug administered via intramuscular (IM) injection. During the home phase, the use of steroids was recommended for class 4 reactions without a complete resolution after nebulized epinephrine.

Administration of nebulized epinephrine: Nebulized epinephrine was administered using a nebulizer (Nebula® Markos, Italy) at a dose of 0.1 mg/kg (maximum dose 3 mg) and was initially diluted in either 3 mL of standard saline solution or in 800 μg of beclomethasone. Since 2008, the protocol has been modified and nebulized epinephrine is always diluted in beclomethasone, since it enhances the local anti-inflammatory effect. Beginning in 2006, nebulized epinephrine was repeated after an interval of 15 to 20 min (a maximum of 2 times), in cases where the initial nebulization did not resolve the symptoms. In addition to epinephrine, the other drugs used to manage the reactions were nebulized beta-2 agonists, oral antihistamines, and nebulized or oral corticosteroids.

Analysis of adverse reactions: Reactions were classified as mild (Clark scale 1-3), moderate (Clark scale 4) or severe (Clark scale 5). Oral itching and mild gastric pain (lasting less than 15 min) were considered slight adverse reactions. However, since they were so common and difficult to evaluate objectively, they were not included in the analysis. The following characteristics were considered: the amount of CM triggering a reaction, the symptoms, the interval between CM administration and a reaction, the treatments required, the interval of the resolution of symptoms (in relation to onset of symptoms and onset of treatment), and the vital parameters (heart rate, blood pressure, peripheral oxygen saturation rate) before and after the treatment with nebulized epinephrine.

Collection of in hospital phase data: All data regarding the reactions during the hospital phase were systematically recorded on the patients' medical records. Continuous data was reported as mean and SD or as median and interquartile range. Categorical data was reported as number and percentage.

Home CM increase: Each patient was discharged with written instructions on how to gradually increase the dose

Table 1 In hospital treatment schedule

Days	Dilution	Dose	CM proteins (grams)
1	1 drop of CM in 10 mL of water every hour	1 drop, 4 drops, 12 drops, 1 mL, 2 mL, 4,5 mL	0.000008, 0.000032, 0.000096, 0.00016, 0.00036, 0.00072
2	4 drops of CM in 20 mL of water every 2 h	1 mL, 3 mL, 6 mL, 10 mL	0.00032, 0.00096, 0.00192, 0.0032
3	20 drops of CM in 20 mL of water every 2 h	1 mL, 3 mL, 6 mL, 10 mL	0.0015, 0.0045, 0.009, 0.015
4	3 mL of CM in 20 mL of water every 2 h	1 mL, 3,5 mL, 7,5 mL, 11 mL	0.004, 0.014, 0.03, 0.044
5	10 mL of CM in 20 mL of water every 2 h	4 mL, 6 mL, 8 mL	0.04, 0.06, 0.08
6	10 mL of CM in 10 mL of water every 2 h	4 mL, 6 mL, 8 mL	0.064, 0.096, 0.128
7	Pure milk every 2 h	1 mL, 3 mL, 6 mL	0.032, 0.096, 0.192
8	Pure milk every 2-3 h	4 mL, 7 mL, 11 mL	0.128, 0.224, 0.352
9	Pure milk every 3 h	10 mL, 12 mL, 15 mL	0.32, 0.384, 0.48
10	Pure milk every 3 h	13 mL, 16 mL, 20 mL	0.416, 0.512, 0.64.

CM, cow's milk.

of CM. The increase in CM was flexible and could be adapted to the patient's tolerance and symptoms by slowing down the rate of increase or keeping it a fixed dose for weeks or even months at a time, in the case of recurring symptoms.

Patients discharged with a single dose of more than 15 mL were instructed to increase by 2 mL every 2 or 3 days until they reached 60 mL, then 5 mL every 2 or 3 days up to a single maximum dose of 250 mL. Patients discharged with less than 15 mL and more than 5 mL were instructed to increase the dose by 1 mL every 5 to 7 days up to 30 mL, and to continue as above. Patients discharged with a dose of less than 5 mL were advised to increase the dose by 0.5 mL every 7 to 10 days. Sublingual SOTI was recommended to children who were discharged with a tolerance of less than 2 mL of CM. From 2001 to 2004, the home phase of CM administration consisted of 2 daily doses. However, as of 2004, the daily double dose was reduced to one dose in order to simplify the protocol, thus improving the families' quality of life. An equivalency table outlining the conversion of CM to cheese and yogurt was provided for the patients, in order to give them the possibility to vary their diet (Table 2).

General recommendations for home CM assumption: Parents were told to keep the child under observation for 3 h following the ingestion of CM and to avoid physical activity during this 3 h period. In case of a respiratory infection, they were instructed to decrease the dose of CM by 30% and in the case of gastroenteritis or asthma by 50%, until a complete resolution of the symptoms was seen. In the case of fever, parents were told to suspend the CM dose for that day. Once the symptoms resolved, they were free to slowly increase the daily dose over a 7 days period until reaching the previous maximum tolerated dose. Patients were instructed to avoid using straws (possible nebulization effect), to skip a dose in the case of tooth extraction or cuts on the tongue, and to avoid hot showers in the 2 h following CM administration. Patients who experienced significant repeated pharyngeal itching or gastric pain were advised to dilute the CM in a substantial amount of fruit juice or soy milk.

Instructions for parents in the treatment of adverse reactions: At the time of discharge parents received oral and written instructions on how to deal with the various reactions associated with the home phase of SOTI. They were trained in how to properly administer the automatic epinephrine injector, and how to use the nebulizer with epinephrine or beta-2 agonists. Parents were given a list of email (for non-urgent communications) and phone contacts (for urgent communications) and encouraged to call with questions or misgivings.

Indications for the treatment of home-phase reactions were as follows:

- Mild rhinitis and persistent pharyngeal itching: 400 μg of nebulized beclomethasone diluted in 2 mL of standard saline solution;
- Mild urticaria: patients under 30 kg–5 mg oral cetirizine, patients over 30 kg–10 mg oral cetirizine;
- Coughing, tightness of the chest, rhinitis, wheezing and/or change in voice: 1mg per 10 kg to a maximum of 3 mg of nebulized epinephrine, followed by nebulized beta-2 agonists in patients with a history of wheezing or with persistent cough or wheezing after epinephrine nebulization; oral steroids (0.15 mg/kg of betamethasone) were also recommended in the case of associated severe urticaria, angioedema and persistent respiratory symptoms. A second epinephrine nebulization after 15 to 20 min was recommended in cases where only a partial response was seen after the initial nebulization.
- Exacerbation of symptoms despite treatment, severe cyanosis, perception of a very severe crisis, loss of consciousness or collapse: IM epinephrine;
- Acute gastric pain: 400 μg oral beclomethasone;
- Recurrent gastric pain: 250 mg oral cromolyn every day (30 min before the ingestion of CM) for approximately one month, at which point the cromolyn was stopped. Diluting the CM in fruit juice or soy milk was also recommended in the cases of recurrent gastric pain.

Documentation of in-home reactions: Parents were asked to record the reactions occurring during the home phase of SOTI. Reactions were divided into 3 categories: cutaneous, gastrointestinal and respiratory. Mild and transient gastric pain (lasting less than 15 min) and oral itching were considered to be insignificant reactions and parents were not asked to report them, unless they were repeated and disturbed the child.

Hospital readmission: Patients who, for whatever reason, stopped the normal CM increase and were still on fixed low doses after 6 to 9 months of home phase SOTI, were offered a 3 day readmission to the hospital in order to attempt a faster and safer CM dose increase in a controlled setting.

Interval between discharge and follow-up: A follow-up call or visit was carried out a minimum of 2 months and a maximum 84 months after discharge.

Specific IgE trend: Patients were encouraged to have yearly blood tests in order to document the specific IgE trends. Specific IgE were measured in all cases of readmission.

Collection of data and definition of results: From the beginning of the study, all the data regarding the reactions reported by parents during the home phase were recorded. Starting in 2008, in order to complete the data, parents were contacted by either phone or email.

Table 2 Equivalency table to be used in the conversion of cow's milk (CM) doses to food doses*

Food	Amount in grams
Low fat yoghurt	103
Whole milk yoghurt	81
Goat's milk	66
CM mozzarella	18
Bel Paese cheese	17
Gorgonzola type cheese	16
Ricotta type cheese	35
Caciotta type cheese (sheep's milk)	13
Asiago type cheese	11
Parmigiano type cheese	10
Emmental type cheese	12
Mascarpone type cheese	46
Gruyere type cheese	10

*100 mL of CM

The type and number of reactions, the quantity of CM, the possible triggers provoking the reactions, Emergency Department admissions and hospital readmissions in order to increase the CM dose, were all reported. Continuous data was reported as mean and SD or minimum and maximum. Categorical data was reported numerically or as a percentage.

Statistical analysis of data: Includes Mann-Whitney U test for mean comparison between 2 groups, a median test for assessing the difference in the median between the 2 groups; Fischer exact test for categorical data. All the analysis were performed using Stata 9 software.

Results

PART 1: In hospital phase

The study involved 209 patients with history of severe CM allergy who presented to the Pediatric Department of the "Burlo Garofolo" hospital in Trieste, Italy between January 2001 and December 2008.Of the 209 patients, 17 were excluded due to the absence of objective reactions. Two of these patients eventually experienced clinically significant reactions during the home phase of SOTI with higher CM doses, but were not included in the analysis. The remaining 192 patients presented with the following reactions during hospitalization:

Mild reactions (Clark scale 1 to 3): 161 reactions in 100 children treated with oral antihistamines or oral betamethasone (in some cases depending on the gravity and type of reaction, treatment was not given).

Moderate reactions (Clark scale 4): 139 reactions in 87 children who were given nebulized epinephrine as a first line treatment, in some cases followed by oral antihistamines, corticosteroids (nebulized beclomethasone or IV methylprednisolone) or nebulized beta 2 agonists.

Severe reactions (Clark scale 5): 5 reactions in 5 children treated with IM epinephrine. Four out of the 5 patients received nebulized epinephrine once, before the IM injection. Two out of 5 had already presented with reactions requiring nebulized epinephrine.

For every group common variables were considered:

- Amount of CM eliciting a reaction, time of onset and the time required for the resolution of the symptoms, length of admission, and CM amount at discharge (Table 3).
- Symptoms and treatments required.
- Vital parameters before and after nebulized epinephrine in moderate and severe reactions.
- Time required for the resolution of symptoms after epinephrine inhalation.

Since 2006, the option of applying a second epinephrine nebulization was introduced in the protocol in cases where there was not a satisfactory resolution of symptoms. The IM epinephrine use in the period from 2001 to 2006 was compared with the IM epinephrine use in the period from 2006 to 2008. From 2001 to 2006, IM epinephrine was used five times in 83 SOTI procedures. However, after 2006, it was not used once in any of the 126 SOTI procedures. Since 2006, 6 children have been treated with 2 consecutive epinephrine nebulizations and one child with 3 nebulizations (after 15 to 20 min).

Part 2: Home phase

Since 2008, 140 patients have been contacted, 8 patients were inaccessible (due to changed address or phone number), while the others are still to be contacted. Patients were contacted beginning with those discharged in 2001.

Table 4 outlines the mean age, male prevalence, mean length of follow up, cause of the initial elimination diet, CM RAST levels pre-SOTI and at follow-up, number of pa-

Table 3 Common data for mild, moderate and severe reactions in hospital

	Mild reactions (Clark scale 1 to 3)	Moderate reactions (Clark scale 4)	Severe reactions (Clark scale 5)
Number of reactions/patients	161/100	139/87	05-may
Mean ages[a] (min-max)	7 years (3-20)	6 years (3-22)	6 years (3-8)
Mean RAST value (SD)	45.5 kUA/L (40,8)	70.8 kUA/L (39,1)	82.9 kUA/L (38,4)
Median RAST class[b] (% patients in 6th class)	4 (24)	5 (45)	5.5 (80)
Patients with asthma/viral wheezing[c], %	52	63	80
Median eliciting CM dose (min-max)	0.9 mL (0.04-40)	3 mL (0.49-60)	0.9 mL (0.39-1.3)
Mean time until the onset of the reaction (interquartile range)	27 min (15-60)	30 min (10-45)	32 min (11-75)
Mean time until the resolution of the main symptoms of the reaction (interquartile range)	64 min (32-94)	20 min (10-30)	19 min (10-25)
Mean length of admission (min-max)	8 days (5-10)	10 days (10-11)	10 days (10-11)
Mean dose of CM at discharge (min-max)	25 mL (12-60)	15 mL[d] (1.5-20)	1.6 mL[d] (0-3)

CM, cow's milk; SD, standard deviation; RAST, radioallergosorbent test; SOTI, specific oral tolerance induction.
[a]The mean age difference between mild and moderate reactions is non-significant (p 0.04)
[b]The median RAST class difference between the mild and the moderate group is significant (p 0.006)
[c]The presence of asthma when comparing the mild group versus the moderate group is significant (p 0.01)
[d]In the moderate and severe group, 6 patients received sublingual SOTI.

tients with asthma/viral wheezing pre-SOTI and at follow-up, and CM dose reached at discharge and at follow-up.

The total number of doses (calculating the daily double dose in the first 3 years) was 89,853; the total number of reported reactions was 891.

Number of reactions for each patient: Of the 132 patients, 48 (36.3%) had no significant reactions (except for oral itching and mild, transient gastric pain that were not recorded), 39 (29.5%) had from one to five reactions, 31 (23.5%) from five to 15 reactions, and 14 (10.7%) had more than 15 reactions.

Percentage of reactions: Out of 891 reactions, 47.7% involved the respiratory tract, 28.8% the gastrointestinal tract and 23.5% were cutaneous.

Factors triggering reactions: Of the 891 reactions, 28.5% were attributed to unknown causes, 27.4% were caused by an increase in the CM dose, 21.9% were due to physical activity, 17.8% were caused by simultaneous infection (especially upper respiratory tract infection), and 4.4% were due to various reasons (antihistamine treatment withdrawal, pollen season in allergic patients, continuous use of dairy products instead of CM, drinking with a straw (2 patients), hot showers, cuts on the tongue (1 patient), and vomiting due to car sickness resulting in nasal inhalation (1 patient).

Late onset reactions: Out of 132 patients, 8 experienced allergic reactions after more than 3 h from CM assumption. Six of these reactions occurred after eating cheese (delayed intestinal absorption could be the likely cause). All were characterized by diffuse urticaria with associated coughing and in 2 cases, mild wheezing. All the reactions were moderate and none required IM epinephrine.

Treatments used: 5 patients (with a total of 6 reactions) were given IM epinephrine, 28 (with a total of 221 reactions) were given nebulized epinephrine, 30 (with a total of 240 reactions) were given nebulized beclomethasone, 24 (with a total of 295 reactions) were given nebulized beta-2 agonist, 24 (with a total of 234 reactions) were given oral betamethasone, 17 (with a total of 92 reactions) were given oral beclomethasone, and 21 (with a total of 294 reactions) were given oral antihistamines.

IM epinephrine treatment: IM epinephrine was required on 6 occasions by five out of 132 patients. Of the five patients, 4 had a class 6 RAST (one had a class 4) and a history of asthma was present in 3 of the 5. Four of the episodes were treated with IM epinephrine as a first-line treatment; 2 were treated after receiving treatment at home.

Temporary stops in CM intake: Five patients had to suspend CM intake for few days (minimum 3, maximum 8 days) due to interfering illnesses (2 had gastroenteritis with dehydration, one contracted Kawasaki disease, one developed appendicitis, and the last was involved in a car crash and sustained significant injuries). All restarted uneventfully with a lower dose (10 to 20% of the previously tolerated one).

Local emergency department admissions: 15 out of 132 patients required 17 admissions to their local Emergency Department (one patient was admitted 3 times) due to the severity of the reactions. Twelve out of 15 patients were admitted despite receiving treatment at home, 2 were treated with IM epinephrine. None were admitted to the intensive care unit.

Table 4 Baseline of patient's characteristics

Number of patients (%) of male patients	132 (67)
Mean age in years (SD), min-max	7.2 (4.03), 3-20
Mean length of follow up in months (SD), min-max	24.2 (19.4), 2-84
Reasons for elimination diet (%)	
Atopic dermatitis	53.8
Episode of anaphylaxis	43.1
A positive RAST or prick test without symptoms	2.3
CM related colitis	0.8
RAST class at entry for 132 patients, %	
Class 6	32.6
Class 5	18.2
Class 4	15.9
Class 3	15.9
Class 2	11.3
Class 1	6.1
Mean value of RAST at entry for 132 patients (SD)	55.1 KuA/L (40.5)
RAST class at follow-up (%)[a]	
Class 6	7.9
Class 5	12.7
Class 4	20.6
Class 3	27.0
Class 2	17.5
Class 1	14.3
Mean value of RAST at follow-up (SD)[a]	27.5 KuA/L (32.1)
Patients with asthma/viral wheezing at entry, %	
Asthma	65.9
Viral wheezing at entry	34.1
Trend of asthma/viral wheezing at follow-up, %[b]	
Improved	63.3
Unchanged	33.4
Worsened	3.3
CM dose at discharge (%)	
Low dose (< 5 mL)	21.4
Moderate dose (5-20 mL)	58
High dose (> 20 mL)	20.6
Tolerance of CM at follow-up (%)	
No tolerance (less than 5 mL) or termination of the protocol[c]	12.4
Partial tolerance (5-149 mL)	23.3
Wide tolerance (150-249 mL)	12.4
Non-restricted diet	51.9

CM, cow's milk; SD, standard deviation; RAST, radioallergosorbent test.

[a]The follow-up data was only available for 63 patients. The CM RAST values decreased in 49 of the 63 patients (a reduction of 3 classes in 4 children, 2 classes in 20 children and 1 class in 25 children). More importantly, there were no increases in the RAST class. Only one child, remained stuck for 6 months on a single dose of 35 mL, and reported an increase in the specific IgE values for whole milk, from 35 to 42 kUA/L in a one year period.

[b]The follow-up data was only available for 30 patients.

[c]Some patients were forced to stop the protocol due to the frequent occurrence of reactions, the refusal by the patient to ingest the CM, and the distress created by the anxiety surrounding the ingestion of the daily CM dose.

Readmissions to Burlo Garofolo hospital: Out of 132 patients, 22 (16.7%) required hospital readmission some months after discharge and 2 children (1.5%) required 2 separate readmissions. These patients remained on a small dose, ranging from 3 to 35 mL of CM. They all demonstrated a significant specific IgE decrease with elevation of specific IgG 4 levels. Nineteen of the 22 patients were able to double their CM dose in just 3 days.

Correlation between IgE levels and home reactions: There was a linear correlation between IgE levels and the number of home reactions. In fact, the higher the IgE class, the greater the risk of reactions.

Correlation between IgE levels and use of nebulized epinephrine: There was a linear correlation between IgE levels and the use of nebulized epinephrine for the treatment of respiratory reactions during the home phase. In fact, the higher the IgE class the greater the risk of using nebulized epinephrine in treatment of respiratory reactions.

Correlation between the amount of CM at discharge and home-phase reactions: There also was a linear correlation between the amount of CM at discharge and the number of home reactions (p = 0,003). The smaller the CM dose at discharge, the greater the possibility of a reaction.

Correlation between CM amount at discharge and use of nebulized epinephrine: There was a linear correlation between the amount of CM reached at discharge and the use of nebulized epinephrine in the treatment of home-phase respiratory reactions. The lower the CM dose, the higher the risk of requiring nebulized epinephrine for home use ($P = .036$).

Correlation between presence of asthma and/or viral wheezing and home-phase reactions: There was no significant correlation between the presence of asthma and/or viral wheezing, and the total number of home-phase reactions or the reactions requiring nebulized epinephrine.

Sublingual SOTI: Four children who could not tolerate CM ingestion were treated with sublingual CM administration. All had tolerated less than 2 mL at the end of SOTI and were instructed to keep 2 mL of CM under the tongue for 3 min and then spit it. All were evaluated with an open challenge after 9 to 12 months. Two of them experienced reactions at a dose lower than 2 mL and stopped SOTI; 2 were able to tolerate higher amounts (6 and 8 mL each) and subsequently move on to the oral SOTI protocol.

Discussion

Using the Burlo Garofolo SOTI protocol, in-hospital SOTI was managed with an acceptable rate of side effects, even in children with very high levels of specific IgE and a history of recent severe reactions. The literature on adverse reactions during SOTI is still limited. Meglio et al.[4] and Patriarca et al.[1] reported a very low incidence of severe reactions, 21 and 59 children respectively, with a mean IgE of 3.9 kUA/L and 32 kUA/L. Skripak et al.[15] during the initial-in-hospital build up phase treated with IM epinephrine 2 out of 13 patients with a mean specific IgE level of 34.8 kUA/L. Nieto et al.[8] described a near fatal reaction in a patient with RAST rating of 6 for CM. In this case, the patient was given 2.5 mL of pure CM on the second day of SOTI, despite the fact that the patient had required IM epinephrine 1 h earlier due to a reaction to the previous CM dose. The authors used a fast paced protocol with a higher dosage of CM in a shorter time when compared to the Burlo-Garofolo SOTI protocol. In this case a 2.5 mL dose of pure CM was administered on the second day of SOTI. One hour earlier the patient had already reacted to the previous CM dose requiring IM epinephrine.

There are some important differences which should be highlighted between the above protocols and that which was used at the Burlo Garofolo Hospital during the hospital phase.

The patient is given a daily dose of antihistamine and the CM dose begins with minute amounts raised slowly over the 10 day period. This approach is prudent, and mirrors the symptoms of the patients in question. Furthermore, the protocol is always suspended on the day of a reaction requiring epinephrine treatment, and restarted the following day with the previously tolerated CM dose, eventually ending with the dose that evoked the symptoms. From the third day of the protocol onward, a minimum interval of 2 h is kept between each CM administration, and on the ninth day of the protocol, the interval is increased to 3 h. A slow initial phase characterizes the Burlo Garofolo hospital protocol. The smallest amount of CM provoking a reaction was 0.014 g (the second dose of the fourth day). This suggests that the protocol can be shortened by using slightly larger doses in the initial period. This approach was chosen to maximize safety, and to allow the beginning of a mucosal "mast cell desensitization". A further important difference between this protocol and the others is reflected in the change of the CM increase according to reactions. In this protocol CM ingestion after moderate reactions or severe diffuse urticaria is always discontinued for that day, restarting the following day from the previously tolerated dose. In this series 67 (34%) patients had a class 6 RAST (specific IgE > 100 kUA/L) and 100 (52%) presented with a history of associated asthma. As expected, there was an association between the incidence of moderate to severe reactions, and RAST class and history of asthma. Even though the total numbers of reactions were considerable, they were easily manageable, responding well to nebulized epinephrine.

This protocol reveals that nebulized epinephrine can play a pivotal role in the management of these patients. Prior to 2006, when only one epinephrine nebulization was administered, 5 patients out of 209 required IM epinephrine. Since 2006, when a second epinephrine nebulization was introduced (after a 15 to 20 min interval in cases where the first nebulization did not resolve the symptoms) not a single patient required IM epinephrine. The same treatment protocol can be adopted either during the oral food challenge performed in a day hospital setting or during the home phase of SOTI with similar results. In a different setting, Järvinen et al.[16] administered IM epinephrine during an oral food challenge to 14 of 50 patients, while Narisety et al.[17] treated 4 of 25 patients with IM epinephrine, during the home phase of SOTI, with a total of 6 injections. In these cases, it is possible that nebulized epinephrine may have reduced the possibility of unnecessary IM epinephrine use. In the International Guidelines, nebulized epinephrine has only recently been introduced as a second line treatment, following IM injection for persistent respiratory symptoms. However, it is well known that respiratory symptoms during anaphylaxis

are more prevalent in children than systemic symptoms, such as hypotension that is typical of adults.[18]

Therefore, it is reasonable to hypothesize that, even with a low level of epinephrine in the blood, the local anti-edema action and the alfa 1-adrenergic effect provided by nebulization plays a major role in the control of symptoms and may arrest the negative chain of respiratory events. The positive effects of nebulized epinephrine were outlined by Hourihane and Warner in 1995[19] who reported that in 20 years of practice the use of IM epinephrine was replaced by nebulized epinephrine. In their study Simons and Estelle[20,21] have shown that most children are unable to inhale epinephrine from a pre-measured dosage nebulizer. However, a thorough search of the literature has not revealed evidence comparing continuous nebulization to pre-measured dosages. The data presented in this article requires cautious interpretation and should not be transferred to any other study or taken out of context. All the reactions occurred in a safe and controlled hospital environment. Nebulized epinephrine should only be used in cases of provoked anaphylaxis, as the event is expected and the epinephrine is ready to be used. Nebulized epinephrine should not be used to replace IM epinephrine in the case of spontaneous anaphylaxis.

The literature regarding the adverse reactions during the home phase of SOTI is still limited and represented by studies with small sample sizes and patients with relatively low RAST values.

Staden et al.[22] used SOTI to treat 25 children with CM and egg allergies. All 25 patients (mean RAST of 10 kUA/L) had mild reactions, and 4 had moderate reactions that were only treated with antihistamines and steroids. In this study the main triggers causing the reactions were: infection, physical activity, pollen allergies and irregular intake of CM. They found that a reduction in the CM dose always prevented side effects. Meglio et al.[5] treated 21 children with CM allergy (mean RAST of 17.1 kUA/L for whole milk). The treatment was successful in 71% of the patients and the reactions were mild requiring only antihistamines. Skripak et al.[15] treated with IM epinephrine during the home phase 2 out of 13 children (mean RAST of 34.8 kUA/L). Patriarca et al.[1] treated 59 patients (mean RAST of 32 kUA/L) with a success rate of 83%. None of the patients experienced any significant side effects, and did not require epinephrine administration or hospitalization. Narisety et al.[17] treated 25 children with a mean RAST of 29.9 kUA/L, who were immediately discharged after an initial introduction to the CM dose in the hospital. Out of 2465 reported administrations of milk, there were 419 mild reactions, 90 gastrointestinal reactions and 21 respiratory reactions. In this study, 5 children received IM epinephrine injections. None of the aforementioned studies reported the use of nebulized epinephrine as a first-line treatment.

This report outlines the progress of 132 children with a mean RAST of 55.1 kUA/L, who were discharged after the 10 day in-hospital rush phase. During the home-phase, the patients received 89,853 administrations of CM resulting in: 256 gastrointestinal reactions, 425 respiratory reactions and 204 cutaneous reactions. Reactions were relatively frequent (one reaction per 100 CM doses), only five children required 6 IM epinephrine injections.

The most significant differences between this study and the others are the large number of children with RAST values > 100 kUA/L (43 patients) and the length of time between the end of the hospital SOTI phase and the follow-up. This study involved the largest sample size documented in the literature, with the longest follow-up and the highest number of patients with high specific IgE levels (over 100 kUA/L).

A large percentage of the reactions were trigged by specific factors, such as infections, physical activity and CM dose increase, but a significant part of the reactions were due to unknown causes. As a result, they were in essence, unpredictable and unexplainable.

Late onset reactions occurring 3 h or more after ingesting CM were rare but reported. Most of these reactions occurred late in the evening after eating cheese. In this case, reactions may be attributed to delayed intestinal absorption. The observation period may need to be extended when CM is being replaced by cheese or yogurt.

Nebulized epinephrine played a pivotal role in the management of home respiratory reactions. Even though these data require cautious interpretation and should not be transferred to other contexts. All the reactions occurred in a controlled environment (patient's home), with parents who kept the children under close observation for 3 h and were able to administer the appropriate treatment for the reaction. It is extremely important to remember that nebulized epinephrine should not be used in the case of spontaneous anaphylaxis as a replacement for IM epinephrine.

Detailed treatment instructions, a list of emergency phone numbers and non-urgent email contacts were the key to the success of the home-phase protocol.

As expected, high IgE levels were the most significant risk factor predicting the adverse home-phase reactions. The other significant risk factor for home reactions was a low CM dose at discharge, which implied frequent and significant reactions during the in-hospital induction phase.

SOTI failed to improve the condition in 12% of patients for a variety of different reasons, including repeated significant reactions, unresponsive gastric pain, refusal by the patient to ingest CM, or severe parental anxiety related to CM intake.

The issue of quality of life is of particular relevance to these patients. Most of them are not eager to consume large amounts of dairy products and an unrestricted diet is a goal for a minority of patients only. However, everyone's main goal is to live fear of a reaction caused by accidental contact with the antigen. The stress related to CM intake, during the SOTI protocol, and its adverse effects can be a significant burden on the patients and their families. It is important to bear in mind that the patient's quality of life should not be compromised to reach at any cost the maximum tolerated dose of CM. This study has some limitations: since slight reactions were not reported by parents, the number of significant reactions may have been underestimated due to incomplete or under-reporting. Further limitations are due to the fact that phone or email contacts were not scheduled at regular intervals.

The specific protocol for SOTI used at the Burlo Garofolo hospital reveals that patients with high specific levels of IgE were able to undergo SOTI successfully with an acceptable rate of side effects. To the best of our knowledge this study reports the largest series of SOTI related reactions in literature. More research is needed in order to compare the diffe-

rent protocols of CM administration and treatment in order to establish the safest and most cost effective protocol. In conclusion the data presented in this article has been the result of a long lasting and well established experience and allows for a reasonable definition of the risk related to SOTI both in hospital and at home. This study shows that SOTI may be applied in the near future outside research protocols, by dedicated and well trained staff.

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