Single dose oral challenges to validate eliciting doses in children with cow's milk allergy

Short title: Single dose milk challenges to validate ED_{05}

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ABSTRACT:

Background: There is increasing interest in the use of eliciting doses (EDs) to inform allergen risk management. EDs can be estimated from the distribution of threshold doses for allergic subjects undergoing food challenges within a specified population. Estimated ED_{05} values for cow's milk (the dose expected to cause objective allergic symptoms in 5% of the milk-allergic population) range from 0.5mg to 13.9mg cow's milk protein. We undertook a single-dose challenge study to validate a predicted ED_{05} for cow's milk of 0.5mg protein.

Methods: Participants were recruited from 4 clinical centres. Predetermined criteria were used to identify patients reacting to 0.5mg cow's milk protein (approximately 0.015ml of fresh cow's milk). Children over 1 year underwent formal challenge to cow's milk to confirm clinical reactivity.

Results: 172 children (median age 6 (IQR 0.7-11) years, 57% male) were included in this analysis. Twelve (7.0%, 95% CI 3.7-11.9%) children experienced objective symptoms that met the predetermined criteria. One participant had mild anaphylaxis which responded to a single dose of adrenaline, the remainder experienced only mild symptoms with no treatment required. We did not identify any baseline predictors of sensitisation which were associated with objective reactivity to the single-dose challenge using 0.5mg cow's milk protein.

Conclusions: These data support an estimated ED_{05} for cow's milk of 0.5mg protein. Values for ED_{05} above 0.5mg for cow's milk protein proposed for allergen risk management need to be reviewed.

Key words

Eliciting dose, single dose challenge, cow's milk, thresholds, Voluntary Incidental Trace Allergen Labelling (VITAL).

Abbreviations:

CMPA	Cow's milk protein allergy
DBPCFC	Double-blind placebo-controlled food challenge
ED	Eliciting dose
IQR	Interquartile range
OFC	Oral food challenge
VITAL	Voluntary Incidental Trace Allergen Labelling

INTRODUCTION

There is increasing interest in the use of routinely-collected clinical data from oral food challenges (OFC) to inform both patient management and allergen risk management in industry, in terms of the level of dietary allergen avoidance required. Eliciting doses (ED) for allergic reactions in 1% and/or 5% of the allergic population (ED_{01} and ED_{05}, respectively) can be used to inform "reference doses", indicating a level of allergen presence above which additional risk management strategies (such as precautionary allergen labelling) are required to protect the allergic population.[1,2] In addition, it has been proposed that dietary advice to food-allergic consumers might be individualized if a particular level of tolerance can be demonstrated at clinical OFC.[3,4]

ED values are generated from OFC data,[5] but many OFC protocols use a starting dose which will trigger symptoms in a significant proportion of patients. For example, the PRACTALL consensus recommends a starting dose of 3mg food protein for OFC,[6] but data suggests that for cow's milk protein allergy (CMPA), this may cause objective symptoms in 10% of allergic individuals.[7] Thus, these data are "left-censored" and cause greater uncertainty when estimating a level of exposure which causes symptoms in a small proportion of the allergic population.[5] Conventional protocols which use incremental doses given every 20-30 minutes also make it difficult to reliably determine the precise dose which has triggered symptoms.[8] In addition, relying on OFC undertaken in routine clinical practice results in selection bias, since many subjects at high likelihood of true clinical reactivity or with a history of prior anaphylaxis are excluded.[6]

CMPA is a major cause of severe and even fatal allergic reactions.[9,10] Data from the United Kingdom have found that cow's milk is the confirmed trigger in over a quarter of anaphylaxis fatalities in children,[11] a pattern that has also been noted in North America and Israel.[12-14] This is probably due to a combination of factors: milk as an ingredient which is ubiquitous in our diets; milk as a high protein food; and lower levels of awareness amongst the public and food business operators that CMPA can cause severe reactions.[15] Estimated ED_{05} values for cow's milk in the literature range from 0.5mg to 13.9mg cow's milk protein.[1,2,7,16,17] We have previously used a novel, single-dose challenge design to validate the ED_{05} for peanut.[3] In this study, we sought to replicate this method in children with cow's milk protein allergy (CMPA), to assess whether current estimates for ED_{05} for cow's milk are valid in terms of allergen risk management.

METHODS

This was a multicentre study which incorporated children with CMPA recruited from 4 clinical centres: Imperial College London - St Mary's Hospital, UK (Imperial); Hospital Clinico San Carlos (HCSC) and Hospital Universitario Infantil Niño Jesús (NJH) in Madrid, Spain; and Cork University Hospital, Ireland (CUH); the specific cohorts are described in Table 1. Exclusion criteria were: Medically unfit for challenge according to local unit OFC guidelines/protocol (e.g. high fever or unwell with intercurrent illness); acute wheeze or poorly controlled asthma symptoms (as defined by clinician judgement with reference to the ICON consensus[18]) or oral corticosteroids within 14 days of OFC; anaphylaxis of any cause in the 4 weeks prior to OFC; antihistamines within 5 days of OFC. In order to minimize selection bias, participation was discussed with all potentially suitable participants and their

families during routine clinic appointments. Subjects with a history of prior anaphylaxis were not excluded. The studies were registered at Clinicaltrials.gov (NCT02216175, NCT02295397).

Single-dose OFC

Protocols were aligned across the 4 centres in order to obtain the same clinical data following 0.5mg cow's milk protein (approximately 0.015ml of fresh cow's milk) administered as a single dose, using the same predefined case definition for objective allergic symptoms. In general, the single-dose challenge was administered as milk powder incorporated into an allergen free chocolate dessert matrix (previously validated for double-blind challenges[19]) or dissolved into flavoured rice "milk" (Table 1). In participants under age 1 year at CUH, the dose was instead administered as diluted (1:7) fresh milk using a syringe (to reduce the risk of a contact reaction to the lips). Routine OFC monitoring was undertaken according to local practice. At two centres (Imperial and NJH), the single-dose OFC constituted the first dose of a formal DBPCFC, and subjects were observed for at least 1 hour prior to the next challenge dose being administered (and longer if there were any non-transient symptoms). At HCSC and CUH, subjects underwent a single (unblinded) administration of 0.5mg protein and were observed for at least 2 hours thereafter.

Criteria for a positive OFC result and case definition

Data collection and case definitions have been previously described.[3] In brief, detailed notes were taken recording all physical or behavioural changes observed or self-reported during the single-dose OFC. Predetermined objective criteria were

used, since published ED_{05} values are predicted on the basis of challenge-associated objective symptoms only.[1-6] The predetermined objective criteria for a positive single-dose OFC result were as follows: 3 or more concurrent wheals of non-contact urticaria persisting for at least 5 minutes; perioral or periorbital angioedema; rhinoconjunctivitis (including sneezing) for at least 5 minutes; diarrhoea; vomiting (excluding gag reflex); or anaphylaxis (with evidence of circulatory or respiratory compromise, such as persistent cough, wheeze, change in voice, stridor, difficulty breathing, and collapse).[20] Transient objective symptoms (rhinoconjunctivitis <5mins, transient mild erythema) were excluded. Subjective symptoms were also recorded. Following completion of the clinical studies, cases were reviewed by at least 2 senior independent investigators and the above criteria were applied to define OFC which met these predetermined objective criteria.

Confirmation of clinical reactivity to cow's milk

In order to avoid the possibility of including participants without CMPA, clinical reactivity was confirmed in participants over 1 year of age at formal oral exposure, typically double-blind placebo-controlled challenge conducted according to international PRACTALL consensus criteria,[6] although some families declined DBPCFC and instead underwent an unblinded challenge under medical supervision which required objective symptoms to be assigned as "positive". Infants (under 12 months) did not undergo OFC, but were included on the basis of physician-diagnosed allergic reaction within 2 months of assessment and IgE sensitisation to milk.

IgE sensitisation

Blood samples were collected from participants prior to OFC. Samples were processed according to the manufacturers' instructions and snap-frozen at -80°C until analysis. Specific IgE to cow's milk and casein were measured using ImmunoCAP (ThermoFisher Scientific, Uppsala, Sweden). Skin prick testing was undertaken according to international guidelines using ALK lancets and commercial extracts (ALK) with 1% histamine as a positive control, and the mean wheal diameter noted.

Statistical analyses

Analyses were planned prospectively. The proportion of participants reacting to 0.5mg cow's milk protein was estimated with 2-sided exact 95% confidence intervals. Baseline characteristics across cohorts were compared using Kruskal-Wallis test since the data were not normally distributed. Receiver operating characteristic (ROC) curves were generated in order to identify possible predictors for reactivity to 0.5mg cow's milk protein. A P value of $< .05$ was considered significant. Assuming a reaction rate of 5% to 0.5mg cow's milk protein, an overall sample size of 150 and 250 would correspond to a lower 95% confidence limit of 2.1% and 2.8% respectively, and an upper confidence limit of 9.8% and 8.7% respectively for the estimated ED_{05}.

Ethical approval

Local approvals were obtained for each clinical centre: Imperial, NHS Human Research Authority reference 15/LO/0286; HCSC, Ethics Committee reference 14/345; NJH, Ethics Committee reference R0003/17; CUH, reference ECM4(N)

03/06/14 and ECM4(U) 04/07/17. Written informed consent was obtained from all participants or their legal guardian, and patient assent was obtained where appropriate.

RESULTS:

267 children were screened for inclusion between August 2015 and September 2020, of whom 182 underwent a single-dose OFC. Ten individuals went on to pass a formal food challenge (i.e. did not react to a minimum of 250ml cow's milk) following the single-dose challenge and were therefore excluded from the primary analysis. Baseline demographics are shown in Table 2. The clinical centre in Ireland predominantly recruited children under age 1 year with CMPA, HCSC recruited infants with new diagnosis of CMPA as well as patients over age 1 year with an existing diagnosis of CMPA, while other centres recruited children with persistent CMPA. Overall, 61 (34%) of the cohort were under age 1 year, (recruited at CUH and HCSC); participants at NJH and Imperial were older ($P < 0.001$, Kruskall-Wallis test). IgE sensitisation was similar across all 4 cohorts in terms of skin prick test wheal, but serum IgE to cow's milk was lower in the CUH cohort ($P = 0.04$), but equivalent across the other 3 cohorts ($P = 0.10$), reflecting the lower age of the included participants.

Clinical reactivity was confirmed at OFC in 69% of participants (and 99% of participants older than 1 year of age). Of these OFC, 84% were DBPCFC conducted according to PRACTALL consensus. The family of an 8 year old male in the HCSC cohort with a history of multiple anaphylaxis events to milk (including bronchospasm to a small piece of chocolate 1 month prior to the single-dose

challenge) declined OFC, but the child was enrolled in a local oral immunotherapy program and experience objective symptoms (generalized urticaria and bronchospasm during updosing), thus confirming clinical reactivity. Eliciting dose at formal OFC to cow's milk in each cohort are shown in Table 2. There were no differences across the cohorts in terms of eliciting dose (P = 0.29), implying that the 4 cohorts were similar to each other in terms of clinical reactivity. We did not observe any correlation between age and eliciting dose at formal challenge (Spearman's r = 0.05, P = 0.59).

Reactions to single-dose OFC using 0.5mg cow's milk protein

Of the 172 single-dose OFC eligible for inclusion, 122 (71%) showed no symptoms (Table 3). 33 (19%) participants reported transient subjective symptoms, while 17 had objective symptoms, of which 12 (7.0%, 95% CI 3.7-11.9%) met the predetermined challenge-positive criteria. These reactions are documented in Table 4. One participant, a 17 year old, experienced mild chest tightness which was associated with bilateral wheeze on auscultation and a 25% drop in peak expiratory flow rate, and mild truncal erythema; these symptoms responded to a single dose of intramuscular adrenaline. Otherwise reactions were mild and did not require treatment. There was no difference in the rate of positive reactions to 0.5mg protein by challenge matrix formulation (P = 0.42, Fisher Exact test) or challenge design for the single-dose challenge (open vs DBPCFC, (P = 0.24, Fisher Exact test). We did not identify any predictors of reactivity to 0.5mg cow's milk protein using ROC curve analysis (Table 5).

These data therefore broadly validate the estimated ED_{05} for cow's milk of 0.5 mg protein (with potential reactions occurring in an interval between 3.7% and 11.9% of the milk-allergic population).

Discussion

Single-dose OFC have previously been used to validate the estimated ED_{05} for peanut, derived from statistical dose-distribution modelling of individual patient threshold doses.[3] In this study, we utilized a similar approach to validate proposed ED_{05} estimates for cow's milk. The observed proportion of patients reacting to 0.5mg cow's milk protein (approximately 0.015ml of fresh cow's milk) with predetermined objective criteria was 7.0% (95% CI 3.7-11.9%). This is within the statistical bounds for the original estimated ED_{05} of 0.5mg cow's milk protein, that would result in 5% of the milk-allergic population reacting with objective symptoms. These data therefore imply that proposed ED_{05} values greater than 0.5mg over-estimate the true ED_{05} for cow's milk.

Population EDs have been proposed by the food industry to establish action levels above which measures are required for risk management, such as the use of precautionary allergen labelling.[23] One such scheme is the Voluntary Incidental Trace Allergen Labelling (VITAL) in Australia. The VITAL Scientific Expert Panel recently updated reference doses for major food allergens, using updated OFC datasets and a new Stacked Model Averaging algorithm incorporating five different statistical models (Weibull, Log Logistic, Log Normal, Log Double Exponential, General Pareto).[2] For cow's milk protein, an ED_{05} of 2.4mg (95%CI 1.3 to 5.0) was proposed, although the action level was based on an ED_{01} of 0.2mg (95%CI 0.1 to 0.5). Prior to the updated VITAL publication, estimated ED_{05} values for cow's milk

derived from the analysis of multiple cohorts varied from 0.57mg to 1.9mg. This variation is mainly due to the uncertainty resulting from a lack of data with respect to low-dose reactors, a phenomenon which particularly affects cow's milk OFC.[2] In the latest analysis by the VITAL Scientific Expert Panel, over 21% of data was left-censored (i.e. patients with CMPA reacted to the first OFC dose) and 75% of included data were derived from OFC where the initial dose was >1.5mg protein (and often significantly more so).[2] In addition, current estimates rely on data from routine clinical challenges where subjects may be excluded (for example, due to prior anaphylaxis or recent reaction) and so the resulting dose-distribution curves may not represent the true allergic population. These are the pivotal justifications for single-dose challenges (such as this study) to validate the estimated EDs at the lower end of the dose distribution curve where data have been lacking.

It is particularly important to have certainty over EDs used for allergen risk management in CMPA. Cow's milk is increasingly ubiquitous in our diets; its protein fractions are soluble and both (liquid) milk and milk powder tend to distribute well in formulations resulting in a homogenous distribution throughout a food product (as opposed to particulate distribution associated with allergens such as nuts).[9,24] It is a frequent cause of severe and even fatal allergic reactions,[9-14] and can be difficult to eliminate from food production lines (for example, those used to produce chocolate-based products) to the extent that a significant proportion of dark chocolate products (made without cow's milk as an ingredient) contain significant levels of cow's milk protein due to shared production.[24,25] In validating the ED_{05} for cow's milk as 0.5mg protein, these data indicate that current estimates for ED_{05} for cow's milk based on population modelling using existing data are too high. Additional, larger

challenge datasets (based on dosing schedules that would allow for interval censoring) are needed to provide more precision to the population dose-distribution modelling around lower ED values.

These data are also relevant to the selection of appropriate protocols for clinical challenges to diagnosis CMPA. In general, the initial doses recommended for DBPCFC under the PRACTALL consensus are 3mg protein,[6] which for most allergens will tend to cause objective symptoms in around 10% of individuals (ED_{10}).[1,7] If the ED_{05} for cow's milk is closer to 0.5mg, then well over 10% of individuals with CMPA would be expected to react to an initial dose of 3mg. Furthermore, many challenge protocols used in clinical practice start with higher doses of 1ml cow's milk (approximately 30mg protein),[26,27] to which around 25% of allergic individuals will react. In the context of OFC where patients may have a higher likelihood of clinical reactivity (for example, prior to commencing allergen immunotherapy), clinicians might therefore wish to choose a lower initial challenge dose to which objective symptoms are unlikely (for example, to build confidence in the patient and their family).

Strengths and Limitations of this study

The international collaboration, robust protocol and the use of predetermined objective, challenge-positive criteria to demonstrate true clinical reactivity (including by OFC in 67%, of which 84% were DBPCFC) are strengths of this study. Infants in one of the Cork cohorts underwent challenges using liquid milk rather than milk powder, however the estimated EDs for liquid milk and milk powder are equivalent.[7] We chose to recruit a significant proportion of participants under 1 year of age,

since CMPA is more prevalent in this age group, but also included teenagers with persistent CMPA who are often excluded from challenge studies. We contend that our participants are very likely to represent the population with CMPA in Europe, since we utilized a recruitment strategy that did not involve the subjective selection of participants by healthcare professionals, nor did we exclude participants with a history of anaphylaxis. Furthermore, the distribution of eliciting doses at challenge in this study are consistent with other published data for cow's milk.[1,2,7,16,17] While there are some very limited data to indicate that adults with CMPA may have a higher threshold than children (on the basis of OFC data from 25 adults and 323 children)[1], we did not identify an age-dependent effect amongst the participants recruited in this study. Just over half of the single-dose OFC were undertaken using a double-blind methodology, with the 0.5mg dose constituting the first dose at DBPCFC (with prolonged observation interval prior to the 2nd dose being administered). We did not observe a significant difference in frequency of objective reaction to 0.5mg cow's milk protein between those who underwent an open challenge and those who had DBPCFC

Conclusions

In summary, we have demonstrated that the ED_{05} for cow's milk is likely to be around 0.5mg protein and certainly lower than some of the proposed values for ED_{05} in the literature. These data demonstrate the need to validate estimated ED values derived from dose-distribution analyses of data in studies not limited by left censoring, in order to identify the most highly dose-sensitive population of patients with food allergy. This will assist regulators, public health agencies, and food business operators in establishing evidence-based approaches to allergen

management as means to protect the food-allergic consumer from accidental exposures.

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Author Contributions:

PJT, JLB and JO'BH conceived the study design. PJT, MVO and ENCM obtained funding. Clinical evaluations were undertaken by PJT, YD, BD, GMM, RNVB, OA, RB, PRR, MFR and JO'BH. PJT led the data analysis and all authors contributed to data interpretation. PJT wrote the first draft of the manuscript. All authors reviewed the manuscript and amended or approved the final version. PJT and JO'BH are jointly responsible for the decision to submit the manuscript for publication.

Declaration of interests

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Table 1: Characteristics of included cohorts

	Ireland	Madrid, Spain		United Kingdom
Centre	Cork University Hospital (CUH)	Hospital Clinico San Carlos (HCSC)	Hospital Universitario Infantil Niño Jesús (NJH)	Imperial College London (Imperial)
Inclusion criteria	History of unequivocal exposure (including accidental) and typical acute allergic reaction within the preceding 2 months and evidence of IgE sensitisation (SPT or sIgE) to cow's milk. OR Positive OFC to cow's milk within 2 months of the single-dose challenge.		History consistent with IgE-mediated allergy to CM AND Positive DBPCFC to cow's milk immediately following single-dose challenge.	
Inclusion age:	0-16 years	Any	6-17 years	
Challenge formulation:	>1yr: Milk powder incorporated into a chocolate dessert matrix <1yr: Fresh cow's milk	Milk powder incorporated into a chocolate dessert matrix	Milk powder dissolved in rice "milk" as part of a DBPCFC	
Blinding for single-dose challenge	Open	Open	Double-blind	
Observation period:	2 hours	2 hours	Minimum 1 h post dose, with no objective symptoms within 2 h	
Clinical reactivity confirmed by:	>1 yr: open OFC <1 yr: allergic reaction within 2m of assessment and IgE sensitisation	Objective symptoms at oral exposure to cow's milk (e.g. OFC, DBPCFC) under medical supervision	Objective symptoms at DBPCFC	

Table 2: Baseline demographics of participants who underwent single-dose challenge to cow's milk

Centre	Ireland CUH	Madrid, Spain HCSC	Madrid, Spain NJH	UK Imperial	Overall
Screened	Age <1 y: 65 >1 y: 11	60	64	67	267
Did not meet inclusion criteria for OFC or refused to participate	13	30	33	9	85
Underwent single-dose challenge	Age <1 y: 57 >1 y: 6	30	31	58	182
Age (median, IQR)	0.6 y (0.5-0.7)	5 y (2-6)	9 y (8-12)	11 y (8-14)	6 y (0.7-11)
Sex (%male)	63%	42%	52%	64%	57%
Excluded due to tolerance to CMPA at subsequent OFC	1	6	1	2	10
Total "valid" single-dose challenges	62	24	30	56	172
Inclusion criteria: • Positive OFC	11/62 (18%)	21/24 (88%)	30/30 (100%)	56/56 (100%)	118/172 (69%)
• Reaction last 2m	51/62 (82%)	3/24 (13%)	n/a	n/a	54/172 (31%)
Serum IgE to: • Cow's Milk (median, IQR)	3.9 (1.2-15.6)	10.8 (1.7-27.6)	20.5 (6.8-87.4)	19.9 (3.0-56.4)	10.3 (2.1-43.9)
• Casein (median, IQR)	1.0 (0.2-8.3)	2.7 (0.35-21.0)	13.0 (2.7-81.1)	14.2 (2.6-52.0)	6.4 (0.8-27.4)
Skin Prick test (mm): • Cow's Milk (median, IQR) • Casein (median, IQR)	7 (5-9) n/a*	6 (5-7) 5 (3-8)	7 (5-8) 6 (5-9)	7 (5-9) 7 (5-9)	7 (5-8) 6 (4-9)
SPT ≥ 8mm (or 6mm for patients under 2 y)[21] OR sIgE ≥ 15kUA/l[22]	43 (69%)	13 (62%)	21 (70%)	42 (75%)	119 (70%)
Eliciting dose at formal OFC (mg protein) • Median • IQR (number)	170 (68-340) (n=11)	1433 (228-1659) (n=21)	444 (44-4444) (n=30)	144 (44-1444) (n=56)	433 (76-1659) (n=118)

*n/a : casein skin test extract not available in Ireland

Table 3: Symptoms experienced to single-dose challenge to cow's milk

Centre	Ireland CUH	Madrid, Spain HCSC	Madrid, Spain NJH	UK Imperial	Overall
Eligible participants (completed OFC)	62	24	30	56	172
Outcome:					
• No symptoms	54	22	18	28	122
• Transient subjective symptoms only	n/a**	0	10	23	33
• Any objective symptoms	8	2	2	5	17
• Objective symptoms*	8	0	1	3	12
• Anaphylaxis	0	0	0	1	1

*objective symptoms which met predefined criteria

** due to participant age, it was not possible to observe study-defined subjective symptoms in the majority of participants at CUH.

Table 4: Participants who met the predetermined objective reactivity criteria/case definition

ID	Centre	Age (y)	Sex	Inclusion	SPT to CM extract (mm)	sIgE to CM (kUA/l)	Time to symptoms	Challenge Symptoms
Ui-14	CUH	0.9	F	Recent reaction in last 2m and sensitised	5	15.4	<5mins	Vomiting
Ui-40	CUH	1.3	F	Recent reaction in last 2m and sensitised	4	3.2	15-20mins	Urticaria, lip angioedema, eczema flare
Ui-66	CUH	2.6	M	Recent reaction in last 2m and sensitised	5	0.95	<5mins	Periorbital angioedema, abdominal pain, eczema flare
Ui-72	CUH	0.2	F	Positive formal OFC	3	7.8	<5mins	Vomiting
U1-26	CUH	0.5	M	Recent reaction in last 2m and sensitised	6	1.36	5-10mins	Lip angioedema, urticaria
U1-29	CUH	0.9	M	Recent reaction in last 2m and sensitised	5	4.42	5-10mins	Urticaria
U1-36	CUH	0.7	M	Recent reaction in last 2m and sensitised	6	ND	5-10mins	Urticaria
U1-50	CUH	0.4	M	Recent reaction and sensitised	5	1.48	5-10mins	Urticaria
S101	Imperial	17	F	Positive DBPCFC	12	29.6	<5mins	Bilateral wheeze, erythema
S129	Imperial	14	F	Positive DBPCFC	13	>100	38mins	Persistent rhinoconjunctivitis
S155	Imperial	10	F	Positive DBPCFC	11	80.4	24mins	Lip angioedema, oropharyngeal pruritus
S214	NJH	8	M	Positive DBPCFC	9	83.4	15mins	Persistent dry cough, vocal hoarseness

ND: not done due to insufficient blood sample

Table 5: Predictors of reactivity to single-dose challenge of 0.5mg cow's milk protein

Biomarker	**Area under ROC curve**	**P value**
sIgE to cow's milk	0.50	0.98
sIgE to casein	0.57	0.56
SPT to cow's milk extract	0.55	0.57
SPT to casein	0.54	0.76