

Table 1

Unadjusted Patterns of Asthma Medication at 12 Months According to Asthma Control Status at 12 Months

Medication	Patients, % ^a		
	Overall (N = 111)	Improved (WC or NWC) asthma at 12 mo (n = 60)	Nonimproved (VPC) asthma at 12 mo (n = 51)
No medication	13.5	13.3	13.7
SABA only (step 1)	6.3	1.7	11.8
SABA plus ICS only (step 2)	27.0	21.7	33.3
SABA and ICS combination ^b (step 3)	6.3	8.3	3.9
SABA and LTRA combination (step 3)	1.8	1.7	2.0
SABA and LTRA only (step 3)	4.5	5.0	3.9
SABA, ICS, and LTRA (step 3)	25.2	30.0	19.6
SABA, ICS, and LTRA combination (step 4)	11.7	15.0	7.8
Controllers only	3.6	3.3	3.9

Abbreviations: ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; NWC, not well controlled; SABA, short-acting β -agonist; VPC, very poorly controlled; WC, well controlled.

^aP = .11 based on the χ^2 test and collapsed categories 5 to 8 (LTRA included in therapy) (ie, 6 categories).

^bFive patients had combination only listed with SABA (not ICS) as additional separate medication during year.

therapy; however, specialty care in our study sample did not independently relate to very poorly controlled asthma at 12 months ($P = .17$) and was underused (22%), comparable to low rates of specialty care noted in studies of low income and Medicaid insured children.⁷ Caregivers who reported worry about medication adverse effects were twice as likely to have children with very poorly controlled asthma than caregivers did not worry about adverse effects, consistent with prior studies.¹⁰ In an actual comparison of corticosteroid exposure using a daily, low-dose inhaled fluticasone lung exposure for a full year (ie, 44 μ g at 2 puffs at twice a day for 1 year = 64.24 mg) vs a 5-day course of oral systemic corticosteroid (60 mg prednisone for 5 days = 300 mg) demonstrates the significantly lower corticosteroid exposure in patients treated with low-dose inhaled corticosteroids.⁷ Caregiver communication about the difference between regular use of inhaled corticosteroids vs rescue oral steroid exposure and the effectiveness of daily inhaled corticosteroid use in preventing acute exacerbations may motivate caregivers to administer daily inhaled corticosteroids rather than rely on intermittent oral steroid courses.

In summary, a substantial number of young children continue to have very poorly continued asthma, despite contact with the medical community. Furthermore, many did not receive guideline-based stepwise therapy. Receipt of asthma specialty care and addressing caregiver worry about medication adverse effects should be major considerations for children with very poorly controlled asthma.

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Evaluation of tryptase after subcutaneous immunotherapy—associated systemic reactions

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Tryptase is an objective marker of mast cell burden and degranulation that is often released in conjunction with other mediators during anaphylaxis, resulting in transient elevation.^{1,2} In addition to elevations in absolute total tryptase levels, a few alternate



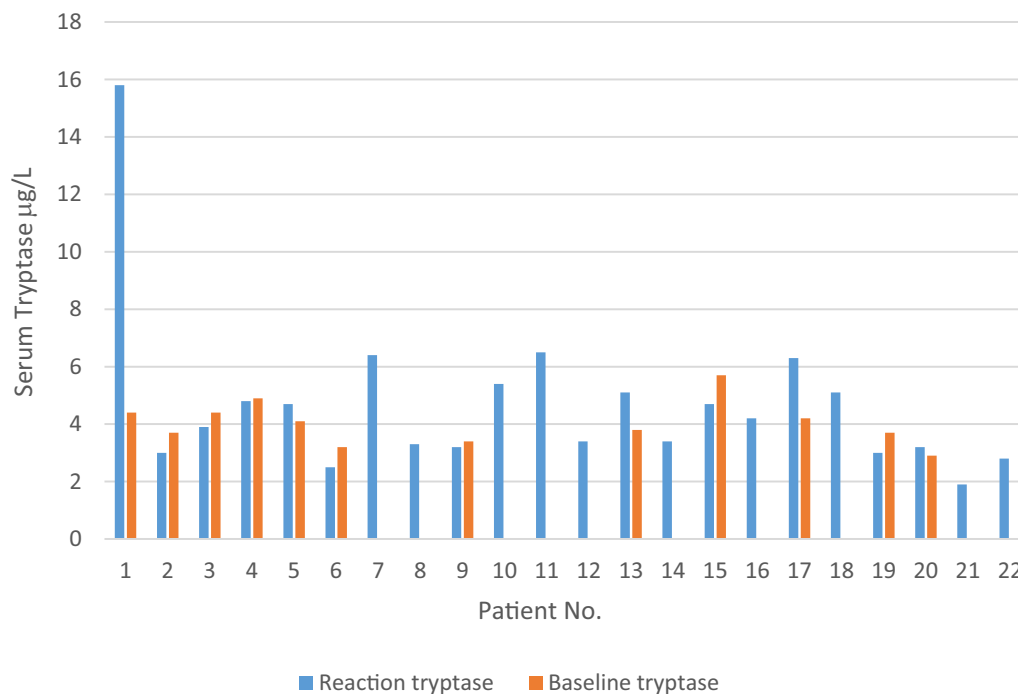


Figure 1. Serum tryptase data of all patients enrolled in the study.

definitions of tryptase levels elevations have been proposed, including an increase of 135%,³ a peak (SD) peak serum tryptase level of more than $2 + 1.2$ times the baseline tryptase level,⁴ and more recently a reaction to baseline ratio of greater than 2.99.⁵ Although tryptase has been measured with anaphylaxis to insect stings, foods, radiocontrast media, and medications, tryptase has not been measured systematically in patients who have had systemic reactions (SRs) to subcutaneous immunotherapy (SCIT). Prior studies measuring tryptase levels in a population of allergic patients receiving aeroallergen immunotherapy only measured baseline tryptase levels rather than tryptase levels at the time of the reaction.⁶ Our goal was to determine whether tryptase levels would remain at baseline in systemic reactions to SCIT as in the case of food allergy reactions or if an increase would be noted as in many other cases of anaphylaxis.

This prospective study was approved by the Wilford Hall Ambulatory Surgical Center Institutional Review Board. Twenty-two adult patients receiving SCIT who experienced SRs in clinic were recruited from a population of 300 patients receiving SCIT from 2014 through 2017. They were receiving build-up or maintenance injections. These recruited patients all experienced SRs during the postimmunotherapy wait period in clinic of 30 minutes and were treated as clinically appropriate with intramuscular epinephrine, antihistamine 1 and antihistamine 2 blockers, β -agonists, or steroids as indicated. Historical details of the reaction, including patient-reported symptoms, physical findings (including vital signs), time of symptom onset and resolution, and interventions, were recorded on a standardized clinic anaphylaxis flow sheet. The severity of reaction was graded at the time of the reaction by the allergist treating the reaction according to the World Allergy Organization (WAO) Subcutaneous Immunotherapy Systemic Reaction Grading System.⁷ No patients requiring transfer to the emergency department were enrolled, thereby limiting our enrollees to patients with mild reactions of grades 1 or 2. A reaction tryptase sample was obtained after a 1-hour postepinephrine observation period with a second baseline tryptase sample drawn 2 to 60 days later. The clinical laboratory analysis of total tryptase was

performed from serum using an immunofluorimetric assay (ImmunoCAP, Phadia, Uppsala, Sweden).

eTable 1 summarizes the patient demographics, reactions, and tryptase levels. The mean patient age was 37 years (range, 23–61 years), and all but 1 patient with venom allergy were receiving aeroallergen SCIT. There was a female (72.7%) to male (27.3%) predominance. For reference, in the United States, approximately 67% of patients receiving aeroallergen SCIT are female.⁸ Ten patients had grade 1 reactions and 12 had grade 2 reactions based on the WAO grading system in place at the time the study was performed.⁷ If instead the proposed updated WAO grading system published in 2017⁹ were used, 4 of our patients may have qualified as having a grade 3 reaction. Seventy-three percent of patients had objective clinical findings, with lower respiratory tract symptoms observed in 45% of reactions. None of the patients experienced hypotension or hypoxia. One intramuscular epinephrine dose of 0.3 mg was administered initially to treat all reactions, and a second dose was administered in 27% of reactions. Ten patients (45%) had a history of at least 1 previous SR. Nineteen reactions (86%) occurred during the build-up phase of immunotherapy. The mean time to resolution after epinephrine was 17.6 minutes. No patients experienced biphasic reactions.

Of the 22 patients enrolled in the study, 12 patients returned to have their baseline tryptase levels drawn. **Figure 1** depicts all serum tryptase values obtained. Only 1 patient with subjective symptoms, labeled as a grade 1 reaction, who was receiving 3 vials of aeroallergen SCIT in the build-up phase, had an elevated reaction tryptase level of 15.8 $\mu\text{g/L}$. This level was considered elevated by all proposed cutoff values of tryptase elevation discussed above. All of the other 21 reaction tryptase levels measured were 6.5 $\mu\text{g/L}$ or below. Each reaction tryptase level that had an associated baseline tryptase level was compared against all 3 proposed cutoff values listed above, and none were elevated by any of the proposed cutoff values aside from the one value of 15.8 $\mu\text{g/L}$. The mean reaction tryptase level was 5.0 $\mu\text{g/L}$, with a range of 2.5 to 15.8 $\mu\text{g/L}$.

Our analysis found that tryptase levels are not typically elevated in mild SRs to SCIT. The reactions described in this study were mild

SRs to SCIT, with most accompanied by objective signs. In the controlled environment of an allergy practice, SRs are expected, monitored, and promptly identified and treated with epinephrine under the guidance of trained allergists. This environment for identifying and treating SRs is clearly different from field anaphylaxis, which typically presents in a delayed fashion in the emergency department setting, often not treated with epinephrine before obtaining tryptase samples or because symptoms resolved.

Our lack of observed elevations in tryptase levels may be because SCIT-induced SRs represent a different physiologic process than the classic IgE-mediated reaction. As outlined in a review article of anaphylaxis by Castells,¹⁰ there are various endotypes of anaphylaxis and a variety of known biomarkers and mediators. We speculate that mechanisms may involve complement anaphylatoxins (eg, C5a), kinins, platelet-activating factor, or lipid mediators, such as urine prostaglandin D₂, which was noted to be elevated in a patient with repeated anaphylaxis who had normal tryptase levels.¹¹

Recently, Dua et al¹² evaluated tryptase levels in patients with suspected peanut allergy during food challenges. An increase in tryptase was seen in 100 of 160 reactions and none in the placebos. Why a good portion of patients with known exposures and reactions do not exhibit elevations in tryptase levels remains to be elucidated and may be attributable to the same physiologic process that explains why elevations were not seen in our mild cases of SCIT-induced reactions as well. In an emergency department study of mediators of anaphylaxis, Lin et al¹³ suggested that the lack of tryptase level elevations in patients with clinical anaphylaxis and elevations in histamine levels suggests basophil involvement.

Other potential explanations for the lack of tryptase elevations in our population include the mild severity of reaction or early intervention with epinephrine. Moreover, the course of immunotherapy itself may modulate the activation of mast cells and subsequent tryptase secretion.

In conclusion, in this first prospective cohort study of SCIT-associated SRs, tryptase levels were not found to be elevated, raising the questions of what mechanisms may mediate these reactions and what effect epinephrine has on tryptase levels. These data suggest future research possibilities that focus on the effects of epinephrine and other mediators on immunotherapy-induced systemic reactions and anaphylaxis in general.

Supplementary Data

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.jana.2019.01.013>.

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Ethanol lock and immunoglobulin load Improving the clinical course of trichohepatoenteric syndrome



A 3-year-old girl with trichohepatoenteric syndrome (THE-S) was admitted for an *Escherichia coli* central catheter-associated bloodstream infection. Her medical history includes chronic diarrhea (baseline of 4–5 loose stools per day) with total parenteral nutrition (TPN) via central catheter, failure to thrive (FTT), renovascular hypertension, iron deficiency anemia, liver impairment, multiple catheter infections, and pneumonia. She was born via cesarean section at an estimated gestational age of 35 weeks because of intrauterine

growth restriction. Immunizations were up to date with the exception of live vaccines. The patient was diagnosed with THE-S during infancy after a neonatal intensive care unit course complicated by feeding intolerance, FTT, intractable diarrhea, TPN dependence, and suspected syndromic features. The results of gene analysis performed when the patient was 4 months of age were positive for a homozygous mutation in the *SKIV2L* gene consistent with diagnosis of THE-S.¹ She has had multiple catheter infections from various pathogens, including *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Salmonella* species, and *Candida* species, which required intensive care hospitalization because of septic shock. This admission accounts for her fifth bloodstream infection in 14 months. Her current central catheter was placed 2 months earlier (a 7F double lumen Broviac). She receives daily TPN infusions run throughout 18 hours. She ingests food, but

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eTable 1

Summary of Patient Demographics, Reactions, and Tryptase Levels

Patient No.	Age, y	Sex	Type of SCIT	Reaction severity	Objective signs	Symptoms	Reaction tryptase, $\mu\text{g/L}$	Baseline tryptase, $\mu\text{g/L}$
1	44	M	A	1	No	Wa, HA	15.8	4.4
2	25	F	A	2	Yes	P, Co	3.0	3.7
3	47	F	A	2	Yes	D	3.9	4.4
4	37	F	A	2	Yes	F, C	4.8	4.9
5	38	F	A	2	Yes	C	4.7	4.1
6	44	F	A	1	No	G	2.5	3.2
7	41	F	A	2	No	CT, C	6.4	NA
8	26	M	A	1	Yes	F	3.3	NA
9	50	M	A	2	Yes	F, C, Co, HA	3.2	3.4
10	27	F	A	1	Yes	U	5.4	NA
11	33	F	A	2	Yes	F, D, An	6.5	NA
12	61	F	A	2	Yes	C, Co	3.4	NA
13	39	F	A	1	Yes	F, U	5.1	3.8
14	26	M	A	2	Yes	C	3.4	NA
15	40	F	V	1	Yes	G, Di	4.7	5.7
16	33	F	A	1	Yes	U, F	4.2	NA
17	23	F	A	1	Yes	F, P	6.3	4.2
18	43	F	A	2	Yes	P, F, U, D	5.1	NA
19	38	M	A	2	No	CT	3.0	3.7
20	39	M	A	2	Yes	CT, W, C	3.2	2.9
21	38	F	A	1	Yes	F, P	1.9	NA
22	32	F	A	1	Yes	C	2.8	NA

Abbreviations: A, aeroallergen; An, angioedema; C, conjunctivitis; Co, cough; CT, chest tightness; D, dyspnea; Di, diaphoresis; F, flushing; G, globus; HA, headache; NA, not applicable (unable to obtain); P, pruritis; SCIT, subcutaneous immunotherapy; U, urticaria; V, venom; W, wheezing; Wa, warmth.