

ORIGINAL RESEARCH—ALLERGY

Prospective analysis of epicutaneous testing for inhalant allergy: Comparison of arm and back subsites with mRAST

Pete S. Batra, MD, Kathy Yappel-Sinkko, CNP, James Bena, MS, Jern-Lin Leong, MBBS, FRCS, Martin J. Citardi, MD, and Donald C. Lanza, MD, Cleveland, OH; Singapore; and St. Petersburg, FL

OBJECTIVES: 1) To compare epicutaneous testing (ET) from four skin subsites (forearm, upper arm, upper back, lower back) and 2) to compare ET to modified RAST (mRAST) for inhalant allergens.

STUDY DESIGN: Prospective clinical trial.

SUBJECTS AND METHODS: Fifty one patients underwent ET at four skin subsites and mRAST to six antigens and positive and negative controls.

RESULTS: The forearm and upper back showed best sensitivity to positive controls and all subsites demonstrated similar specificity to negative controls. The forearm and upper back demonstrated best sensitivity and specificity for most antigens. No statistically significant differences were noted for antigen sensitivity and specificity for the four subsites. ET and mRAST agreed best on *D. farinae* and timothy grass and least on short ragweed and dog epithelium.

CONCLUSION: This study confirms that forearm and upper back demonstrate very good sensitivity and specificity for positive and negative controls and most tested antigens. This has important diagnostic implications for clinical practice of inhalant allergy.

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Since its initial description by Lewis and Grant in 1926,¹ skin prick, or epicutaneous testing (ET), has become a common diagnostic modality for defining the allergic profile. ET has been found to be reliable and convenient; it is more sensitive and reproducible than scratch testing and correlates better with intradermal testing.² The US Council of Allergy, Asthma, and Immunology³ and the European Academy of Allergology and Clinical Immunology⁴ have recommended ET as the preferred method for diagnosis of IgE-mediated allergic disease.

Multi-test II (MTII) (Lincoln Diagnostics, Inc., Decatur, IL) is a disposable, sterile, epicutaneous test applicator that allows for simultaneous application of eight antigens.⁵ MTII has gained popularity secondary to convenience, reproduc-

ibility, safety, and patient acceptance.⁶ Despite its advantages, MTII is a semi-quantitative test compared to modified radioallergosorbent testing (mRAST) or intradermal testing (IDT). A recent study by Levine et al evaluated the correlation between RAST and MTII.⁷ They demonstrated poor positive correlation between results with overall average agreement of 67.86%, although agreement for negative tests was 95.15%.

Data available on the variation in regional skin responses and optimal site for skin testing is sparse at best.^{8,9} Alexander and McConnell initially demonstrated the superior reactivity of the back compared to the forearm in 1930.⁸ Nelson et al also have reported on the more notable skin response on the back compared to the forearm for histamine and cat allergen.⁹ One must also account for the regional skin differences in mast cell distribution.¹⁰ Since sensitized mast cells release histamine in response to skin testing, regional variations in mast cell concentration could potentially impact the results seen with skin testing at various sites. Despite this data, some clinicians test for multiple allergens at varied skin subsites simultaneously and report results as equivalent measures of allergy.

The goal of this study was twofold: 1) to compare ET responses from four skin subsites (forearm, upper arm, upper back, lower back) and 2) to compare ET responses to mRAST for inhalant allergens. The study hopes to define the optimal site for placement of ET utilizing the MTII, while taking into consideration its correlation to mRAST.

METHODS

Fifty-one adult subjects with history of inhalant allergies were prospectively recruited for inclusion in the study from March 2005 to August 2006. The study setting was an academic center–affiliated regional rhinology practice

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Table 1
MTII wheal size and grade and the corresponding mRAST class

MTII wheal size	MTII grade	mRAST class
<5 mm	0	0
5-6 mm	2+	I, II
7-10 mm	3+	III
>10 mm ± pseudopod formation	4+	IV

(Cleveland Clinic Beachwood). All subjects were recruited from the clinical practices of Pete S. Batra, MD, and Martin J. Citardi, MD, of the Section of Nasal and Sinus Disorders at the Cleveland Clinic Head and Neck Institute. Institutional Review Board (IRB) approval was obtained prior to commencing with the study; all subjects signed an IRB-approved consent form prior to enrollment.

Inclusion criteria were as follows: 1) age between 18 and 65 years, 2) good general health, and 3) two or more symptoms (sneezing fits, itchy eyes, watery eyes, itchy nose, runny nose, itchy palate) suggestive of inhalant allergy, or one symptom suggestive of inhalant allergy with positive family history for inhalant allergy.

Exclusion criteria were as follows: 1) age less than 18 or greater than 65 years, 2) poorly controlled asthma, 3) pregnancy, 4) beta-blocker usage, 5) history of dermatographism, 6) history of latex sensitivity, 7) history of immunotherapy, 8) history of systemic reactions to skin testing, and/or 9) recent viral upper respiratory infection.

Complete history and head and neck examination were performed on all patients. Demographic data, clinical symptomatology, past medical history, concomitant sinonasal diagnoses (chronic rhinosinusitis, sinonasal polyposis, septal deviation, inferior turbinate hypertrophy, and history of previous sinus surgery), and family history of allergies were recorded in all patients.

MTII was initially performed on the forearm to six antigens and positive and negative controls. All reactions were recorded at 20 minutes. If no significant local or systemic reaction was noted after the initial testing, upper arm, upper back, and lower back were sequentially tested in all subjects.

Six inhalant allergens were tested, along with positive and negative controls: timothy grass (100,000 BAU/mL), short ragweed (1:20 w/v), *Dermatophagoides farinae* (10,000 AU/mL), cat dander (10,000 BAU/mL), dog epithelium (1:20 w/v), *Alternaria tenius* (1:10 w/v), positive control (histamine phosphate 2.75 mg/mL), and negative control (buffered saline in 50% glycerin). The antigens were standardized as per international standards set forth through the International Union of Immunological Societies' Committee for Allergen Standardization. The antigens and the controls were purchased from ALK-Abelló (Round Rock, TX).

Subsequent to ET, all patients were sent to the lab for blood testing. The mRAST utilized for testing in this study was ImmunoCap (Phadia AB, Portage, MI).

The reactions for MTII for the four subsites were recorded by wheal size in mm for the antigens and the controls. The wheals were converted to a scale of 0, 2+, 3+, and 4+ (Table 1). The responses for the mRAST were recorded as Class 0, I, II, III, and IV. The correlation between MTII and mRAST was determined as demonstrated in Table 1.

Statistical Analysis

Summaries of the demographic values were constructed using means and standard deviations for continuous measures. For each site, the sensitivity (using positive controls) and specificity (using negative controls) were calculated along with 95% confidence intervals. Pairwise comparisons of the sensitivities and specificities were performed using McNemar's test. Sensitivity and specificity for the six antigens by ET was determined by presuming mRAST to be the gold standard for the purposes of statistical analysis.

Weighted kappa statistics were used to evaluate agreement between skin subsites and between mRAST and each site for all allergens. Confidence intervals for each kappa statistic were calculated. As a reference, a kappa of 0.4 to 0.6 indicated moderate agreement, 0.6 to 0.8 indicated good agreement, and greater than 0.8 indicated near-perfect agreement. All tests assumed use of a 0.05 significance level.

RESULTS

The mean age of the 51 patients was 38 years with a male:female ratio of 0.8:1. Table 2 summarizes the distri-

Table 2
Demographic and clinical factors for the 51 patients

Measure	Level	N	Percentage
Gender	Male	23	45.1%
	Female	28	54.9%
CRS	No	28	54.9%
	Yes	23	45.1%
SNP	No	46	90.2%
	Yes	5	9.8%
Septal deviation	No	10	19.6%
	Yes	41	80.4%
ITH	No	31	60.8%
	Yes	20	39.2%
Previous FESS	No	40	78.4%
	Yes	11	21.6%
FH allergy	No	22	43.1%
	Yes	29	56.9%

CRS, chronic rhinosinusitis; SNP, sinonasal polyposis; ITH, inferior turbinate hypertrophy; FESS, functional endoscopic sinus surgery; FH, family history.

Table 3
Positive and negative controls and the corresponding sensitivity and specificity for the four MTII subsites

Site	Positive control		Negative control		Sensitivity (95% CI)	Specificity (95% CI)
	+	–	+	–		
Forearm	47	4	2	49	0.92 (0.82, 0.97)	0.96 (0.87, 0.99)
Upper back	46	4	3	48	0.92 (0.81, 0.97)	0.94 (0.84, 0.98)
Lower back	43	8	2	49	0.84 (0.72, 0.92)	0.96 (0.87, 0.99)
Upper arm	33	18	1	50	0.65 (0.51, 0.76)	0.98 (0.90, 1.00)

bution of demographic and clinical factors among this cohort of subjects.

Table 3 demonstrates the results for the positive and negative controls for the four MTII subsites. The frequencies of positive and negative responses at each site are shown, along with the sensitivity and specificity. Utilizing the McNemar's test, the forearm ($P < 0.001$), upper back ($P < 0.001$), and lower back ($P = 0.024$) demonstrated statistically superior sensitivity compared to upper arm. No

statistical differences were noted for sensitivity among forearm, upper back, and lower back. No statistically significant differences were noted for specificity between the four subsites.

Table 4 demonstrates the sensitivity and specificity for MTII subsites and mRAST for timothy grass, short ragweed, *D. farinae*, cat dander, dog epithelium, and *A. tenius*. Using the mRAST as the gold standard, sensitivity for MTII was highest for timothy grass and cat dander and lowest for

Table 4
Sensitivity and specificity for MTII subsites for the six antigens

Antigen	Site	RAST positive		RAST negative		Sensitivity (95% CI)	Specificity (95% CI)
		+	–	+	–		
Timothy grass	RAST	13	0	0	38		
	Forearm	13	0	6	32	1.00 (0.77, 1.00)	0.84 (0.70, 0.93)
	Upper arm	13	0	6	32	1.00 (0.77, 1.00)	0.84 (0.70, 0.93)
	Lower back	13	0	8	30	1.00 (0.77, 1.00)	0.79 (0.64, 0.89)
	Upper back	13	0	6	32	1.00 (0.77, 1.00)	0.84 (0.70, 0.93)
Short ragweed	RAST	13	0	0	38		
	Forearm	11	2	7	31	0.85 (0.58, 0.96)	0.82 (0.67, 0.91)
	Upper arm	10	3	9	29	0.77 (0.50, 0.92)	0.76 (0.61, 0.87)
	Lower back	10	3	11	27	0.77 (0.50, 0.92)	0.71 (0.55, 0.83)
	Upper back	12	1	10	28	0.92 (0.67, 0.99)	0.74 (0.58, 0.85)
<i>D. farinae</i>	RAST	21	0	0	30		
	Forearm	18	3	3	27	0.86 (0.65, 0.95)	0.90 (0.74, 0.97)
	Upper arm	19	2	4	26	0.90 (0.71, 0.97)	0.87 (0.70, 0.95)
	Lower back	19	2	2	28	0.90 (0.71, 0.97)	0.93 (0.79, 0.98)
	Upper back	18	2	4	26	0.90 (0.70, 0.97)	0.87 (0.70, 0.95)
Cat dander	RAST	16	0	0	35		
	Forearm	16	0	7	28	1.00 (0.81, 1.00)	0.80 (0.64, 0.90)
	Upper arm	16	0	6	29	1.00 (0.81, 1.00)	0.83 (0.67, 0.92)
	Lower back	16	0	10	25	1.00 (0.81, 1.00)	0.71 (0.55, 0.84)
	Upper back	16	0	7	28	1.00 (0.81, 1.00)	0.80 (0.64, 0.90)
Dog epithelium	RAST	14	0	0	37		
	Forearm	5	9	1	36	0.36 (0.16, 0.61)	0.97 (0.86, 1.00)
	Upper arm	5	9	2	35	0.36 (0.16, 0.61)	0.95 (0.82, 0.99)
	Lower back	5	9	4	33	0.36 (0.16, 0.61)	0.89 (0.75, 0.96)
	Upper back	5	9	1	36	0.36 (0.16, 0.61)	0.97 (0.86, 1.00)
<i>A. tenius</i>	RAST	7	0	0	44		
	Forearm	4	3	3	41	0.57 (0.25, 0.84)	0.93 (0.82, 0.98)
	Upper arm	6	1	2	40	0.86 (0.49, 0.97)	0.95 (0.84, 0.99)
	Lower back	4	3	4	40	0.57 (0.25, 0.84)	0.91 (0.79, 0.96)
	Upper back	7	0	4	40	1.00 (0.65, 1.00)	0.91 (0.79, 0.96)

Table 5
Weighted kappa comparison for the four MTII subsites

Allergen	Forearm vs upper arm (95% CI)	Forearm vs lower back (95% CI)	Forearm vs upper back (95% CI)	Upper arm vs lower back (95% CI)	Upper arm vs upper back (95% CI)	Upper back vs lower back (95% CI)
Timothy grass	0.96 (0.64, 1.00)	0.96 (0.63, 1.00)	0.96 (0.64, 1.00)	0.97 (0.64, 1.00)	0.99 (0.66, 1.00)	0.96 (0.63, 1.00)
Short ragweed	0.92 (0.63, 1.00)	0.89 (0.58, 1.00)	0.91 (0.60, 1.00)	0.95 (0.64, 1.00)	0.93 (0.62, 1.00)	0.94 (0.61, 1.00)
<i>D. farinae</i>	0.92 (0.60, 1.00)	0.94 (0.62, 1.00)	0.90 (0.57, 1.00)	0.95 (0.62, 1.00)	0.94 (0.61, 1.00)	0.95 (0.61, 1.00)
Cat dander	0.96 (0.66, 1.00)	0.87 (0.54, 1.00)	0.91 (0.58, 1.00)	0.88 (0.56, 1.00)	0.93 (0.60, 1.00)	0.92 (0.58, 1.00)
Dog epithelium	0.78 (0.63, 0.94)	0.75 (0.58, 0.92)	0.82 (0.68, 0.97)	0.75 (0.58, 0.92)	0.90 (0.75, 1.00)	0.74 (0.58, 0.91)
<i>A. tenuis</i>	0.80 (0.63, 0.96)	0.80 (0.64, 0.96)	0.65 (0.47, 0.83)	0.74 (0.57, 0.92)	0.82 (0.64, 1.00)	0.60 (0.42, 0.79)

dog epithelium and *A. tenuis*. The specificity for MTII was comparable for all antigens, ranging from 71% to 96%. Using the McNemar's test, no statistical differences in sensitivities or specificities were noted for the six antigens for the four skin subsites.

Table 5 illustrates the weighted kappa comparison for the four MTII subsites. The weighted kappa statistic for timothy grass, short ragweed, *D. farinae*, and cat dander was equal to or greater than 0.8, indicating near-perfect agreement for the four skin subsites. The weighted kappa statistic for dog epithelium and *A. tenuis* ranged between 0.6 and 0.8, indicating good agreement, except for upper arm and upper back comparison for dog, with kappa value of 0.9.

Table 6 illustrates the weighted kappa statistic for the four MTII sites and mRAST. Best agreement was noted for *D. farinae* (0.78 to 0.82) and timothy grass (0.74 to 0.78), indicating good to near-perfect agreement and good agreement, respectively. Poorest agreement was noted for short ragweed (0.4 to 0.56) and dog epithelium (0.45 to 0.57), indicating moderate agreement.

DISCUSSION

Timely recognition and accurate diagnosis are central to the optimal management of patients with inhalant allergies.

Inherent to the challenge of defining the allergic profile in suspected patients is the fact that there is diversity of opinion among experts as to which testing methodology is most accurate for diagnosis of inhalant allergy. Indeed, Poon et al have questioned whether there is a true gold standard for diagnosis of inhalant allergies.¹¹ In vitro techniques, such as RAST and mRAST, allow for measurement of serum allergen-specific IgE but can produce false-negative and false-positive results in patients with and without allergy, respectively.¹² In vivo techniques, including ET and IDT, may also lack the sensitivity and specificity to be deemed gold standards.¹¹ In general, correlation between patient symptomatology and diagnostic tests ranges between 50% and 80%.^{13,14}

ET has gained widespread popularity for allergy diagnosis given its convenience, reliability, safety, and patient acceptance. Nonetheless, ET is subject to variability by multiple extrinsic and intrinsic factors.¹⁵ One such important factor is the regional response to skin testing; data available on the variation in regional skin responses to antigens is sparse at best. Previous studies have suggested that reactivity on the back is greater.^{8,9} Despite this data, the arm is commonly employed as the primary site for ET.

Several important observations stem from this study. The forearm and upper back were noted to have better sensitivity (92%) compared to lower back (84%) and upper arm (65%).

Table 6
Weighted kappa statistic for the four MTII sites compared to mRAST

Allergen	RAST vs forearm (95% CI)	RAST vs upper arm (95% CI)	RAST vs lower back (95% CI)	RAST vs upper back (95% CI)
Timothy grass	0.78 (0.51, 1.00)	0.77 (0.50, 1.00)	0.75 (0.47, 1.00)	0.74 (0.47, 1.00)
Short ragweed	0.56 (0.32, 0.81)	0.49 (0.24, 0.73)	0.40 (0.14, 0.66)	0.46 (0.20, 0.72)
<i>D. farinae</i>	0.81 (0.52, 1.00)	0.81 (0.51, 1.00)	0.82 (0.52, 1.00)	0.78 (0.48, 1.00)
Cat dander	0.67 (0.39, 0.94)	0.73 (0.45, 1.00)	0.63 (0.34, 0.92)	0.68 (0.39, 0.97)
Dog epithelium	0.51 (0.31, 0.71)	0.45 (0.24, 0.65)	0.48 (0.26, 0.69)	0.57 (0.37, 0.77)
<i>A. tenuis</i>	0.50 (0.34, 0.66)	0.69 (0.52, 0.85)	0.47 (0.30, 0.63)	0.75 (0.57, 0.92)

The histamine response on the forearm, upper back, and lower back was statistically superior to upper arm. This data compares favorably to a recent report by Carr et al.¹⁶ A total of 6864 pricks on the arm and back were performed in 13 subjects; they reported sensitivity and specificity for the MTII at 93% and 99%, respectively. This is very similar to the 92% sensitivity and 96% specificity on the forearm and 92% sensitivity and 94% specificity on the upper back noted in this study.

The four skin subsites fared well when comparing the responses to the six antigens. The weighted kappa statistic for timothy grass, short ragweed, *D. farinae*, and cat dander was equal to or greater than 0.8, indicating near-perfect agreement. For dog epithelium and *A. tenuis*, the weighted kappa statistic ranged between 0.6 and 0.8, indicating good agreement. No statistical differences were noted for the four skin subsites using the McNemar's test, indicating statistically comparable responses at all four subsites.

Levine et al have retrospectively compared MTII and mRAST to 14 antigens in 20 subjects.⁷ The correlation for positive results was poor, with an average agreement by antigen of 56.26% and overall agreement of 67.86%. The overall negative agreement was 95.15%, with an average agreement by antigen of 83.99%. In contrast, the sensitivity of the MTII compared favorably to mRAST for most antigens in this study. Sensitivity for MTII was highest for timothy grass and cat dander, as 100% of the mRAST antigens were identified by MTII, and lowest for dog epithelium at 36%, with only 5 of the 14 mRAST-positive responses identified by MTII. For this part of the statistical analysis, mRAST was presumed to be the gold standard, as it is readily quantifiable for validating serum-specific IgE elevations in the blood.

Weighted kappa statistic allows for a more accurate comparison of the antigen responses, since it evaluates for agreement beyond chance between sites and for the MTII and mRAST techniques. Traditional correlation methods only measure associations and do not evaluate agreement. Thus, the nonstandardized scales (mm wheal size and serum IgE levels) were transformed to standardized results to evaluate for a much stronger hypothesis comparing the two testing methods. Weighted kappa statistic demonstrated best agreement for *D. farinae* (0.78 to 0.82) and timothy grass (0.74 to 0.78), indicating good to near-perfect agreement and good agreement, respectively. Good agreement was also noted for cat (0.63 to 0.73), while moderate to good agreement (0.47 to 0.75) was noted for *A. tenuis*. Lowest agreement was noted for short ragweed (0.4 to 0.56) and dog epithelium (0.45 to 0.57), still indicating moderate agreement.

Definitive explanations for the observed differences on the arm and back in this study are difficult to assert, but regional differences in mast cell distribution may be an important factor. Additionally, variations in skin thickness, penetration, and/or microvasculature may help account for the discrepancy. Van Strien and Korstanje quantified skin blood flow by laser Doppler flowmetry after application of

patch tests.¹⁷ They noted a significant difference between the upper and lower backs, with stronger responses on the upper back. Differences in cutaneous biology are also present. Weber et al have performed pattern analysis of human cutaneous mast cell populations by total-body surface mapping and demonstrated an increase in mast cells in superficial skin vs subcutis and peripheral vs central sites.¹⁸ Specifically, they demonstrated higher concentration of mast cells in the forearm region and back of head compared to the trunk. Thus, the variation in skin subsite responses observed in this study may be, in part, explained by differences in mast cell distribution throughout the body.

It is important to remember skin testing measures the response at an organ site different than the site of symptoms. Thus, at best, it represents an indirect measure of the nasal and/or ocular response to inhaled allergens. Nasal provocation testing (NPT) aims to identify and quantify the clinical relevance of inhalant allergies. Thus, it may represent more accurately the end organ response to respiratory allergens and has been advocated as the potential international gold standard by Gosepath et al.¹⁹ However, due to prohibitive cost, this has only been used largely in the research environment in the United States.

Operator variables must also be factored into the analysis. Numerous medications can suppress the skin response to histamine and antigens. Great care was taken to avoid these confounding medications prior to skin testing, including first- and second-generation antihistamines, H₂ blockers, and tricyclic antidepressants, for specified periods of time. Antigen extract potency may also vary, and only standardized antigens were utilized in the study. Inter-operator variability can impact test responses and a single advanced practice nurse was utilized for administering the testing and reading the responses.

The results in this prospective analysis have important clinical implications in the practice of inhalant allergy. The low sensitivity for the histamine response on the upper arm is significant. Although the antigen responses on the upper arm were comparable to the other subsites, the histamine response serves as reference for the tested antigens. Suboptimal histamine response would call into question the validity of the antigen response and may result in repeat and unnecessary testing. Thus, based on this data, the upper arm should be avoided for ET with the MTII device. In general, comparing by skin subsite, forearm and upper back demonstrated best correlation to mRAST for most antigens and highest sensitivity and specificity compared to the other skin subsites. Thus, these two subsites may allow for a more robust assessment of inhalant allergy in suspected patients.

CONCLUSION

Prospective study was undertaken to compare responses of MTII on the forearm, upper arm, upper back, and lower back to six antigens; this was also compared to mRAST

results. The analysis demonstrated superior responses to positive and negative controls and most tested antigens on the forearm and upper back, indicating that these are preferred sites of skin testing. MTII and mRAST agreed best on *D. farinae* and timothy grass and least on short ragweed and dog epithelium. This data has important implications in the clinical practice of inhalant allergy; these testing variabilities should be taken into account before labeling patients as being positive or negative to specific antigens.

AUTHOR INFORMATION

From the Section of Nasal and Sinus Disorders, Head and Neck Institute (Drs Batra and Citardi and Ms Yappel-Sinkko) Cleveland Clinic Foundation and Section of Biostatistics, Department of Quantitative Health Sciences (Mr Bena), Cleveland Clinic Foundation; Singapore General Hospital (Dr Leong); and Sinus & Nasal Institute of Florida, P.A. (Dr Lanza).

Corresponding author: Pete S. Batra, MD, Section of Nasal and Sinus Disorders, Head and Neck Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue, A71, Cleveland, OH 44195.

E-mail address: batrap@ccf.org.

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AUTHOR CONTRIBUTIONS

Pete S. Batra, MD, principal investigator, study design, conduct of study, protocol and manuscript writing; **Kathy Yappel-Sinkko, CNP**, co-investigator, patient testing, data collection, data entry; **James Bena, MS**, study design, statistical analysis, manuscript writing; **Jern-Lin Leong, MBBS, FRCS**, patient testing, manuscript writing; **Martin J. Citardi, MD**, co-investigator, study design, protocol and manuscript writing; **Donald C. Lanza, MD**, co-investigator, study design, protocol and manuscript writing.

Drs Citardi and Lanza are senior co-authors.

FINANCIAL DISCLOSURE

Pete S. Batra, MD: GlaxoSmithKline, speaker's bureau (June 2007-present).

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