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Diagnostic accuracy of patch testing based on clinical response to contact allergen restrictions in allergic contact dermatitis

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Key words

Allergen avoidance; contact allergy; diagnostic accuracy; dermatitis; patch test.

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Impact statement

The PT had moderate diagnostic accuracy. A positive test could be useful as a screening, but it does not confirm the clinical relevance of a contact allergen.

Summary

Background. *Patch testing (PT) is used to identify substances that cause allergic contact dermatitis (ACD). However, the clinical effects of allergen restrictions following PT have not been thoroughly investigated. This study aims to assess the diagnostic accuracy of PT in patients suspected of having ACD.* ***Methods.*** *Prospective study. PT was performed in patients with clinical diagnosis of ACD. Patients with a positive PT (case group) had a strict restriction of the suspected substance for one month. In patients with negative patch testing (control group), allergen restriction was based on clinical history. Clinical reduction (CR) of at least 50% in disease activity (CR50%) after one month of allergen restriction was considered clinically relevant. Total control was defined as clinical reduction of at least 90% (CR90%).* ***Results****. Of 400 patients, 66.2% had a positive PT. The sensitivity of PT according to CR50% was 84%, specificity 47%, PPV 53%, and NPV 81%. Only 10.5% of patients achieved CR90%.* ***Conclusions.*** *The PT had moderate diagnostic accuracy. It could be useful as a screening, but a positive result should be confirmed with controlled allergen restriction. The low number of patients who achieved a 90% CR requests to reconsider the allergens included in PT and the mechanistic processes of the disease.*

Introduction

Contact dermatitis is a common, noninfectious inflammatory skin condition resulting from direct or indirect skin contact with exogenous substances. It typically is revealed by the appearance of lesions, usually eczema, following exposure to various substances (1-3). Contact dermatitis is often divided into irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD is a nonspecific skin response to direct chemical skin damage involving the release of inflammatory mediators, while ACD is a hypersensitivity reaction to allergens, including immune responses (4). It has been observed that some professions, due to the greater

contact with certain substances, carry a higher risk of developing ACD. For instance: construction workers, hairdressers, and healthcare professionals, develop ACD secondary to potassium dichromate, PPD, and rubber chemicals, respectively (5, 6).
Diagnosis obstacles arise in establishing the contribution of exogenous substances in the skin disease. The clinical relevance of a substance in ACD can be defined in different ways, but in general we must consider clinically relevant those substances that worsen or cause a patient's symptoms upon exposure and symptoms improves when contact with the substance stops. Patch testing (PT) has been positioned as the gold standard test to establish the diagnosis of ACD and to identify suspects substances potentially associated with the disease (7, 8). Most studies have evaluated the diagnostic performance of PT based on clinical history but in this way is not possible to assess correctly false positives (positive PT without clinical relevance) and this could explain the wide variation in diagnostic performance observed for the PT in the different studies (9); sensitivity ranges from 50-90% and specificity from 40-90% (10, 11). Additionally, several studies suggest a high frequency of positive PT (20-40%) in the general population, which can be explained by an underdiagnosis of the disease or a high frequency of false positives (12, 13).
Clinical guidelines suggest that once the identification of a suspicious substance producing the ACD is made with PT, strict restriction must be carried out (14-17). If the suspected substance is the cause of the problem, with restriction measures there should be significant control of the symptoms, however, there are currently no specific clinical scales to assess ACD activity. This article evaluates PT performance by comparing the ACD activity before and after allergen-restriction using the skin extension and skin severity as clinical parameters. This prospective evaluation offers several advantages over other studies allowing assessment not only of PT´s diagnostic accuracy but also the clinical impact of allergen restrictions in ACD. Additionally, in this study we propose a clinical scale to measure ACD severity.

Materials and methods

Study design

Prospective study with case and control assignation. The main objective of the study was to evaluate the diagnostic performance of the PT in ACD patients. Participants with a positive PT (case group) had a strict restriction of the suspected substance for one month and not change in topical or systemic therapy during evaluation period. Patients with negative PT (control group), allergen restriction was based on clinical history. ACD diagnosis was established by dermatologists or allergists. The gold standard for evaluating PT diagnostic performance was the clinical response after one month of restriction (**figure 1**).

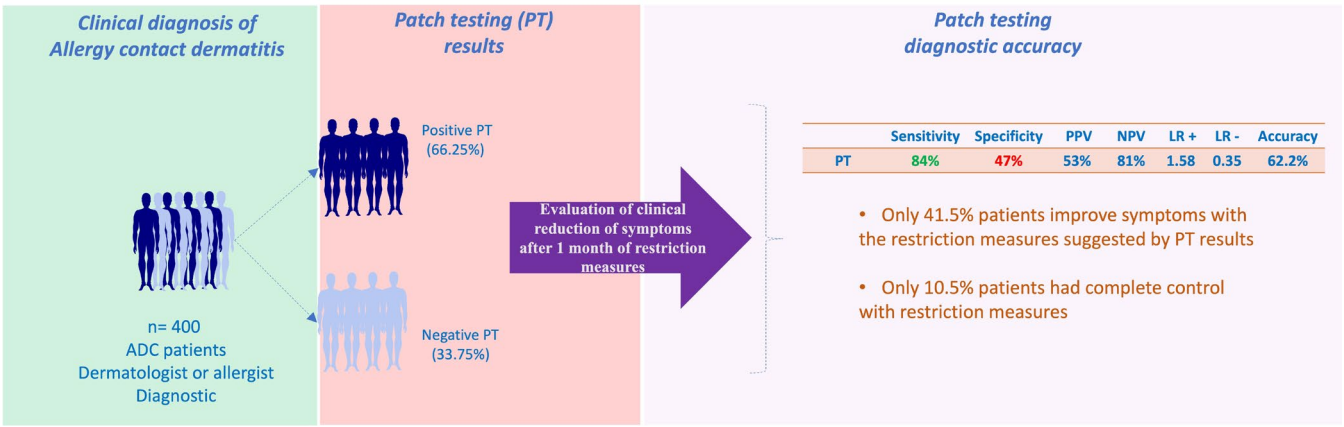
Patient selection

The recruitment of patients was carried out on three centers located in Colombia. Patients with no age limit were included. Patients should not be taking drugs that could affect the interpretation of the test. Patients with other skin conditions were excluded.

Patch testing

The PT was performed in accordance with international recommendations using a standard series (LA-100) from "Chemotechnique diagnostics" laboratory (**table IS**). Forty allergens, enclosed in plastic chambers were applied to each patient back. After forty-eight hours, the patches were removed for a first reading. The second reading was performed at 96 hours. A positive test was determined based on the results of the second reading (15, 16,

Figure 1 *- To evaluate the diagnostic accuracy of patch testing (PT) in patients with clinical diagnosis of allergy contact dermatitis (ACD) we use the clinical response to contact allergen restriction as comparator.*



18). To mitigate measurement biases, a consensus on interpreting the patch tests was reached during an initial meeting with all investigators. Each test was independently reviewed by at least two researchers, with discrepancies resolved by a third researcher.

Assessment of clinical response

To our knowledge, there is not a specific scale to evaluate the activity of the ACD. We evaluated clinical response of allergen restrictions using three parameters; extent of affected skin, pruritus intensity, and investigator global assessment (IGA); the assessment tool is presented in **table I**. This evaluation was carried out one day before and 30 days after allergen restriction. We considered significant clinical reduction in symptoms (CR), a decrease of at least 50% (CR50%) in the assessment tool.

On the first visit, a photographic record of the patient's entire skin surface was captured. Weekly, patients documented their skin's evolution through weekly photographs. Throughout the one-month follow-up, patients were recommended to use only skin hydration as active treatment to assess the clinical response to the restriction. If the intensity of the lesions was not tolerated and required the use of additional topical treatment, the primary outcome was measured the last day before initiating pharmacotherapy.

Considering that there is not specific clinical tool for assessing ACD, we conducted an exploratory analysis to evaluate the correlation between the proposed assessment tool in this study, the quality of life according to the dermatological index of quality of life (DLQI) and the Atopic Dermatitis Disease Control (ADCT).

Restriction measures

All patients underwent a training to identify potential sources of exposure for each substance. Patients could contact the centers to resolve any questions during the restriction month. The objective was to achieve a total restriction during the study period, however this is not always feasible, so at the end of the month the patients were asked to rate from 0 to 100% the rigor of the restrictions to each allergen compared to the period before the study started.

Statistical analysis

Considering the study's objective, we opted not to perform matching between case and control groups. Based on the frequency of exposure reported in previous studies (1, 12, 13) and case definition, at least 80 patients in each group were sufficient to assess diagnosis performance. We pre-established a goal of 400 patients for a greater precision of the results.

Results of the index test (PT) and the reference standard (Contact allergen restriction) were classified in a 2 × 2 contingency table. From this table, standard measures of discrimination, including sensitivity, specificity, predictive values, and likelihood ratios, along with unitary measures (correct classification accuracy), were calculated with 95% confidence intervals. Patients with missing data regarding PT results or the clinical response to the restriction measures were excluded.

Bioethical considerations

The study protocol was approved by the institutional ethics committee (code IN57-2021 # acta 177 Hospital "Alma Mater de Antioquia" and University of Antioquia) and is in line with the Helsinki declaration. Each participants signed to indicate their informed consent.

Results

General characteristics

Of 418 who accepted to participate, a total of 400 patients were included (**table II**). 10 patients were excluded because follow-up

Table I *- Evaluation score.*

	Extension	Pruritus	IgA
CR90%	Reduction ≥ 90%	Reduction ≥ 90% or less than 3 points in pruritus intensity (0 to 10 points).	Reduction ≥ 90% or less than 1 point
CR50%	Reduction ≥ 50%	Reduction ≥ 50% or less than 3 points in pruritus intensity (0 to 10 points).	Reduction ≥ 50% or less than 1 point
No control	Reduction was under 49%	Reduction ≤ 49% (or increase)	Reduction ≤ 49% (or increase)

Extension, pruritus, and investigator global assessment (IGA) were evaluated before and after allergen restriction; criteria for clinical reduction 50% (CR50%) and clinical reduction 90% (CR90%) were based on these three parameters. Pruritus was evaluated with the question "From 0 (none) to 10 (high intense) How was itch in the past 24 hours?". IGA points were defined: 0 clear: NO inflammatory signs of Contac dermatitis (no eczema, no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post inflammatory hyperpigmentation and/or hypopigmentation may be present. 1 Almost clear: Barely perceptible eczema erythema, barely perceptible induration/population, and/or minimal lichenification. No oozing or crusting. 2 Mild: slight but definite eczema, slight but erythema (Pink), slight but definite induration/papula, and/or slight but definite lichenification. No oozing or crusting. 3 Moderate: Clearly perceptible eczema, clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing or crusting may be present. 4 Severe: Marked eczema, marked erythema (Deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

was not possible and 8 were excluded after identifying a second skin disease that could affect the interpretation of the results. The female gender was predominant (67.8%); most of the patients were older than 18 years (n = 378, 94.5%) (**table II**). Most patients had an office work (47.25%). A total of 190 (47.5%) patients had lesions in skin areas of high clinical and emotional impact (face, hands, or intimate area); 91 (22.75%) patients with lesions in these high impact areas had also lesions in other body sections. In most patients the PT was done during the first year of the symptom's onset.

Table II *- General characteristics.*

	n = 400 (100%)
Females	271 (67.8%)
Age (years)	48 min 8 max 90
< 18	22 (5.5%)
19 To 40	115 (28.75%)
41 to 60	190 (47.5%)
> 60	73 (18.25%)
Asthma	24 (6%)
Rhinitis	123 (30.7%)
Chronic urticaria	0
Atopic dermatitis	0
Workplace	
Home	70 (17.5%)
Office	189 (47.25%)
Health	13 (3.25%)
Construction	7 (1.75%)
Rural work	24 (6%)
Cosmetic work	18 (4.5%)
Other	79 (19.75%)
Affected body area*	
Face	72 (18%)
Hands	86 (21.5%)
Intimate area	32 (8%)
Other	301 (75.25%)
Disease duration before patch test (years)	
1 year	243 (60.75%)
1 to 5 years	83 (20.75%)
More than 5 years	74 (18.5%)

Continuous variables were presented as median and range (minimum, maximum). *Some patients (22.75%) had more than one affected body area. Unemployed patients were categorized in the area where they spent most of their time.

The most frequent potential allergen triggers according to clinical history were nickel (58%), palladium (43%), and fragrances (18%). Some patients associated certain substances from work (23%) or recreational activities (18%).

Patch testing results

A total of 265 (66.25%) patients had a positive PT. In 142 (53.6%) patients more than one allergen was positive in the PT. Nickel was the most prevalent followed by palladium (**table III**). We explore the relationship between workplace and sensitization patterns but there was not significant association with any of the most common allergens.

Clinical response

Of the 265 (66.25%) patients with positive PT, 166 (41.5%) had a CR50% after performing the restriction measures and in 140 of these patients the allergens were detected with the PT (test sensitivity 84%, 95%CI 77.9% to 89.5%). Twenty-one patients with negative PT had clinical improvement following allergen restrictions based on clinical history and five patients with negative PT who did not carry out an adequate restriction despite the recommendations had a spontaneous improvement. A total of 234 (58.5%) patients had no improvement with restriction

Table III *- Patch testing results.*

	n = 400 (100%)
Positive path test	265 (66.25%)
Monosensitization	123 (46.4%)
Polysensitization	142 (53.6%)
Negative path test	135 (33.75%)
Most common allergens according to the patch test	
Nickel sulphate	110 (41.5%)
Palladium	92 (34.71%)
Fragrance mix	25 (9.43%)
Thimerosal	23 (8.67%)
Cobalt chloride	18 (6.79%)
Neomycin	13 (4.9%)
Potassium dichromate	12 (4.52%)
Methylisothiazolinone	12 (4.52%)
Methyl-dibromo glutaronitrile	11 (4.15%)
Formaldehyde	10 (3.7%)
Others	118 (44.52%)

From the 40 contact allergens probed, only 5 have positivity in at less 5% of patients.

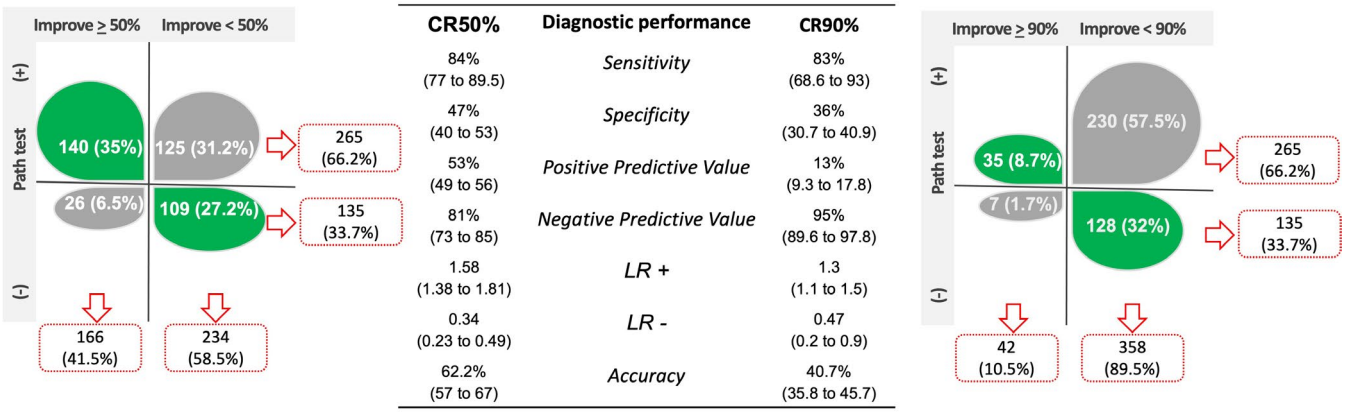
measures; in 109 of them the PT was negative (47% specificity 95%CI 40% to 53.1%).
When evaluating compliance with the restriction measures, there were no statistically significant differences between those who clinically improved *versus* those who did not improve clinically in the case group (improvement 83%, 95%CI 75 to 94% *versus* no improvement 81%, 95%CI 72 to 91% p = 0.7) nor in the control group (improvement 83% 95%CI 75% to 94% *versus* no improvement 81%, 95%CI 72 to 91% p = 0.7).
According to CR50%, the PT correctly classified 249 patients (diagnostic accuracy 62.2%) (**figure 2**). The positive and negative predictive value were 53% and 81% respectively. A positive PT increases the probability of CR50% after restriction (OR 4.6 95% CI 2.8 – 7.6).
According CR90%, the PT had lower diagnostic performance; only 42 (10.4%) patients reached this level of control.

Exploratory comparison of CR assessment tool, DLQI, and ADCT
When we compared the results of CR score and DLQI, 83% of patients with DLQI over 10 points had no control according to CR score; 71% of patients with DLQI under 10 points had CR50% according to CR score.
When we compared the results of CR score and ADCT, 89% of patients with ADCT over six points had no control according to CR score; 68% of patients with ADCT under six points had CR50% according to CR score. This exploratory evaluation suggests a good sensitivity of CR score to evaluated in ACD patients' different domains of clinical control.

Discussion and conclusions

Since its description by Jadassohn (18), done more than 100 years ago, PT is considered the gold standard test for ACD diagnostic (19). The PT is performed using a series of allergens, which means that multiple tests are performed at the same time, which increases the risk of false positives and decision making difficult regarding which restraint measures are relevant in each patient (12, 19, 20). Different studies have evaluated the diagnostic accuracy of PT but to our knowledge this is the first prospective study evaluating diagnostic accuracy based on the clinical result of restriction measures.
Our study presents interesting results: 1) the sensitivity of the test was moderate and according to clinical impact we found that the specificity of the test is low, with a high number of false positives. 2) Many patients achieved partial improvement (CR50%) after restriction measures but few achieved complete improvement (CR90%). 3) A potentially specific clinical scale is proposed to evaluate disease activity in patients with ACD.
Clinical relevance of PT must always be carefully evaluated because positive reactions may indicate sensitization but not significant relation with the disease. The request for unnecessary restrictions can have a high burden on the quality of life of patients. Studies from unselected population from North American and European found that the median prevalence of positive PT to at least one contact allergen was 21.2% for North American and 27% for Europe (range 12.5% to 40.5%) with a higher prevalence in women (35.5% *vs* 17.1%) (12, 13). The interpretation of these studies in the light of our results seems to indicate that the PT has a high frequency of false positives, which explains its high sensitivity but low PPV. Therefore, PT alone cannot confirm the diagnosis of ADC and its clinical relevance needs to be evaluated. However, there is no global agreement on what clinical relevance is in ACD (21); the clinical relevance has been analyzed mainly retrospectively based on the clinical history, environment, work, hobbies of the patient, and identification of the positive allergen in these contexts using PT (22), but little has been studied pro-

Figure 2 *- Diagnostic performance of patients according to clinical reduction ≥ 50% (CR50%) or ≥ 90% (CR90%).*



The parenthesis in table are 95% confidence interval of each parameter; LR: likelihood ration.

spectively regarding the identification and elimination of the allergen and the subsequent evaluation of the clinical response, which constitutes the main strength of this work. Gallo *et al*. (23) evaluated through telephone calls the remission of contact dermatitis in patients who carried out restriction measures based on the result of PT. The authors report a high rate of remission or significant improvement (85.2%, 431/506), much higher than that observed by us. However, the authors performed avoidance measures in only 506 patients out of 1,397 who had a positive test, based on the clinical probability that the PT was relevant, confirming our observation that the PT is useful as a screening test, but a positive result does not confirm clinical relevance. PT allows us to identify substances potentially related to the clinical manifestations of our patients, however, multiple factors can induce false positives or false negatives (*e.g*., new allergens not included in the test; positive sensitizations to old exposures currently not relevant, *etc*.). Therefore, the PT should be accompanied by a detailed anamnesis and an evaluation of the possible substances to which the patient is exposed to identify what additional substances should be included in the test that are not present in the standard battery. These points highlight the importance of carrying out controlled avoidance measures to define the clinical relevance of the substances identified with the PT.

Bearing in mind that there is no validated specific clinical tool for ACD, we used three parameters to talk about clinical relevance. According to these parameters, patients improved with restriction measures (CR50%), but few achieved complete control (CR90%). Considering that contact dermatitis is defined by the appearance of lesions upon exposure by a contact, the low rate of complete control could be explained because the patients did not strictly carry out the avoidance measures or maybe, we must reconsider what we understand about the disease mechanism. Traditionally, it has been proposed that the mechanism for ACD is caused by a type IV delayed hypersensitivity reaction in the skin and is initiated when an allergen enters the skin and activates the innate and adaptive immune system cells (24). However, experimental studies suggest that depending on the allergen multiple mechanisms exists in ACD, and inflammatory profiles could be present in ACD patients even without contact exposition (24, 25). These results imply that the PT could have different diagnostic performance according to the type of allergen exposed and the underlying mechanism (1, 26).

Recent advances in the understanding of contact dermatitis mechanisms suggest that ACD is more complex than previous thought (4, 27). Our results indicate that despite strict restriction, complete remission occurs in a minor number of patients with ACD diagnosis. A high number of patients reach a CR50% but less than 20% of patients reach CR90%. This fact can have two explanations; 1) the PT series that we use does not detect all the allergens involved in the patient's illness. 2) Contact allergens can aggravate the disease but are not always a decisive factor in its persistence, indicating underlying skin damage that can persist even after removing environmental triggers. Despite the fact that this second hypothesis has little evidence and goes against what we popularly accept in ACD, it is in line with the new knowledge about the pathogenesis of the disease (4, 27) and it is similar to what we now know in other skin diseases like atopic dermatitis (28).

ACD in children has been scarcely studied and in general evaluations have been done in patients with atopic dermatitis. Similar as what has been reported in other studies, we observed that the prevalence of ACD diagnosis was higher in patients over 30 years. We explored if there was difference in diagnostic performance of PT in patients under 15 years but there was not significant difference to what we report in adults.

Rajagopalan and Anderson demonstrated a benefit in most domains of the DLQI in a group of contact dermatitis patients who underwent the PT compared with a group who did not (29). They observed that even in patients with a negative test, ruling out the causality of common contacts can lead to an improvement in quality of life. However, in this study it is not clear the clinical impact that restriction to suspected substances has on quality of life.

Our study has some weaknesses and strengths. The low frequency of sensitization and/or exposure to some tested substances makes their correct evaluation difficult. Additional series, patient materials or photopatch test could increase the sensitivity and relevance of the test, mostly in occupational cases. Nevertheless, we included a large number of patients, so we consider that the evaluation was adequate for most of the allergens tested. Additionally, patients were selected because they required a standard PT as a first evaluation because there was little likelihood that their ACD was photoinduced. A possible limitation of the study is the restriction time. We chose a month of avoidance considering the skin cycle (30); however, we cannot rule out that a longer period of time would be better to evaluate the clinical improvement. Despite we educated patients to contact allergen restriction measures, we could no guarantee 100% that all patients fallowed restriction measures all the time. However, considering the support network offered and the weekly contact with the clinical centers, we believe that the restrictions were stricter than what most patients do in real life. Other strengths of the study were its prospective design and the photographic evaluation that allowed us to objectively evaluate the changes reported by the patient. One of the limitations of the PT is the different interpretation of the results since it depends on the experience of the person doing the PT. To reduce this variance in the study, each test was interpreted by at least two clinicians trained in PT, so this potential measurement bias was controlled.

In conclusion, the PT can be useful to identify substances that aggravate ACD, however the high frequency of false positives makes it necessary to evaluate the relevance with adequate assessment

of allergen restriction. The low number of patients who achieved a clinical improvement greater than 90% makes it necessary to reassess the concepts of the disease regarding its pathophysiology.

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Contributions

JSC, MVL: methodology, project administration, resources, software, supervision, validation, visualization, writing - review & editing. LAR: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing - original draft, writing - review & editing. SDZ, JMM: conceptualization, data curation, formal analysis, investigation, methodology, resources, software, validation, visualization, writing original draft.

Conflict of interests

The authors declare that they have no conflict of interests.

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