Factors associated with treatment outcomes after intravesical hyaluronic acid therapy in women with refractory interstitial cystitis: A prospective, multicenter study

Ching-Pei Tsai[a], Jenn-Ming Yang[b], So-Jung Liang[c], Yi-Hao Lin[d], Wen-Chu Huang[e,f], Tzu-Yin Lin[g], Chun-Shuo Hsu[h], Fei-Chi Chuang[i], Man-Jung Hung[j,*]

[a]Department of Obstetrics and Gynecology, Taichung Veterans General Hospital, Taichung, Taiwan, ROC; [b]Department of Obstetrics and Gynecology, Shuang Ho Hospital, Taipei, Taiwan, ROC; [c]Department of Obstetrics and Gynecology, Wan Fang Hospital, Taipei Medical University, Taiwan, ROC; [d]Division of Urogynecology, Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Medical Center, Chang Gung University College of Medicine, Taoyuan, Taiwan, ROC; [e]Division of Urogynecology, Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan, ROC; [f]Department of Nursing, Mackay, Medicine, Nursing and Management College, Taipei, Taiwan, ROC; [g]Department of Obstetrics and Gynecology, Taipei City Hospital, Branch for Women and Children, Taipei, Taiwan, ROC; [h]Department of Obstetrics and Gynecology, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan, ROC; [i]Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan, ROC; [j]Department of Obstetrics and Gynecology, Chung Shan Medical University Hospital; Department of Obstetrics and Gynecology, School of Medicine, Colleague of Medicine, Chung Shan Medical University, Taichung, Taiwan, ROC

Abstract

Background: Bladder instillation of hyaluronic acid (HA) is an acceptable treatment for bladder pain syndrome/interstitial cystitis (BPS/IC). The treatment is limited by a high proportion of non-responders (~30%–40%). Here, we aimed to evaluate predisposing factors associated with treatment outcomes.

Methods: This is a prospective multicenter study. We enrolled a total of 137 (out of 140) women with refractory IC. They all underwent a standard protocol of 6-month intravesical HA therapy (initial 4 weeks, once weekly, followed by once monthly). To assess the outcomes, we used the pain Visual Analog Scale (Pain-VAS), Interstitial Cystitis Symptom and Problem Index (ICSI & ICPI), and a scaled Global Response Assessment (GRA).

Results: The age of patients was 47.6 ± 27.5 (range 24–77) years. We found statistically significant improvement ($p < 0.001$) in the Pain-VAS and the ICSI & ICPI scores both after the initial 4-weekly instillations and at the end of 6-month treatment. Those who reported moderate/marked improvement on GRA at the 2 follow-up visits were considered responders: 39.4% (n = 54) at the first follow-up, and 59.9% (n = 82) at the second follow-up. No remarkable side effect was noted. After statistical analyses, treatment outcomes on GRA were positively associated with baseline functional bladder capacity and with Pain-VAS scores. The initial treatment responses optimally ($p < 0.001$) predicted final treatment outcomes (McNemar).

Conclusion: Intravesical HA therapy is safe and effective for most (~60%) of our patients with refractory IC. Functional bladder capacity and Pain-VAS scores before treatment, and the early treatment responses are helpful predictors of treatment outcomes.

Keywords: Bladder pain syndrome; Hyaluronic acid; Interstitial cystitis; Intravesical therapy; Treatment outcome

1. INTRODUCTION

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a urinary disorder characterized by frequency, urgency, and pelvic pain in the absence of other identifiable pathology, like infection or bladder cancer. Its diagnosis is based on chronic symptoms after ruling out infection and other less common conditions.[1,2] Despite decades of basic and clinical research, the etiology of BPS/IC (BPS) remains obscure. This disease likely has a multifactorial etiology.[3] The current accepted theory of its cause is injury or dysfunction of the glycosaminoglycan (GAG) layer (defensive mucosal lining) that covers the urothelium.[3] Today, hyaluronan, the salt of hyaluronic acid (HA) is one of the most commonly used GAGs for intravesical treatment for BPS/IC patients refractory to conventional therapy.[4]

In clinical practice, most patients report symptomatic improvements during the first month of treatment, and then gradually, the improvements subside during the subsequent maintenance period.[5] In fact, not all symptoms of all patients

*Address correspondence. Dr. Man-Jung Hung, Department of Obstetrics and Gynecology, Chung Shan Medical University Hospital, 110, Section 1, Chien-Kuo North Road, Taichung 402, Taiwan, ROC. E-mail address: adiposehung@gmail.com (M.-J. Hung).

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resolve dramatically after such therapy. The treatment hence faces major limitations because of the high proportion (~30%–40%) of nonresponders.[6–12] Such diverse treatment success could be related to individual variations in the severity of disease symptoms, differences in the protocol of instillation, and methods of assessing outcome measures.

Here, we aimed to evaluate changes of symptoms after intravesical therapy using HA solution and determine factors associated with treatment outcomes. Results could provide better estimates on the treatment outcomes.

2. METHODS

2.1. Study design

This was a prospective, multicenter study conducted over a 2-year period (from March 2015 through March 2017) involving 9 tertiary referral hospitals in Taiwan. Institutional Review Board and Ethics Committee approved this clinical trial (CE15042B). The diagnosis of BPS/IC was based on symptoms, cystoscopic findings, and the exclusion of other diseases according to the ESSIC criteria.[1] A total of 140 patients included with the characteristics of BPS/IC had previously been treated conservatively with oral medications, with or without bladder hydrodistention, and were all refractory to treatment that necessitated referral. The oral medications included pentosan polysulfate, nonsteroid anti-inflammatory drugs, tricyclic antidepressants and anticholinergics.

2.2. Clinical assessment

The symptoms and bothering issues at baseline and after intravesical HA treatment were assessed using the following: (1) 10-point pain visual analog scale (pain-VAS), (2) the Interstitial Cystitis Symptom Index (ICSI) and Problem Index (ICPI),[13] and (3) a short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12).[14] In addition, a 3-day voiding diary was used to record and assess functional bladder capacity, frequency, and nocturia. At each time point of study, uroflowmetry was used to measure the maximum flow rate, voided volume, and postvoid residual volume.

Under anesthesia, cystoscopy with hydrodistention was carried out to confirm the diagnosis of IC. Patients with typical Hunner's ulcers were specifically recorded and a biopsy study done. The volume of saline infused (at 80–100 cm H_2O) was recorded as the anesthetic bladder capacity. During saline release, cystoscopic findings of glomerulations, with or without the findings of Hunner's ulcers, suggested IC characteristics were recorded according to the Interstitial Cystitis Data Base (ICDB) study recommendations.[15] A comprehensive, multichannel urodynamic study was done optionally for some patients.

2.3. Treatment protocol and outcome measures

The treatment started 4 weeks after the cystoscopic diagnosis. Before therapy, patients gave informed consent for our study. The standard protocol was performed with 4 weekly bladder instillations, each with 40 mg/50 mL of a commercial HA solution (CYSTISTAT, Mylan Institutional, Galway, Ireland) followed by 5 similar monthly instillations. After the urethra was anesthetized with 2% lidocaine jelly, the HA solution was instilled into the bladder via a 10-French urethral catheter. Patients voluntarily retained the solution in their bladders for 60 minutes before allowed to void. Prophylactic antibiotics were not routinely used, but standard sterilization techniques were conducted before catheterization.

After treatment, the scaled (+3 to –3) Global Response Assessment (GRA) was used to evaluate the perception of patients on their overall changes in bladder conditions (symptomatic outcomes). Treatment efficacy was determined based on the GRA results. Patients were asked to rate their bladder symptoms compared with baseline on a 7-point centered scale as markedly (+3), moderately (+2) or slightly improved (+1), no change (0), to slightly (–1), moderately (–2), and markedly worse (–3). Those who reported on GRA with moderate or marked (≧+2) improvements at the 2 follow-up visit were considered treatment responders. Early response was evaluated at 1 month, while late response was assessed at 6 months. Functional outcomes were assessed by comparing parameters from a 3-day voiding diary and uroflowmetry with residual urine determined before and after treatment.

2.4. Statistical analyses

Clinical data are presented as mean ± SD or percentage according to the nature of variables. Repeated measure ANOVA was used to compare differences on the pain VAS scores, ICSI and ICPI scores, and PISQ-12 scores before and after treatment. Univariate analysis was used to defect the differences in patient characteristics between treatment responders and nonresponders. Finally, the generalized estimating equation (GEE) was used to determine which parameters had correlated with treatment outcomes. The McNemar test was used to determine inter follow-up consistency in treatment responses. Differences were considered statistically significant with p values <0.05. Statistical analyses were carried out using SAS 9.2 statistical software (SAS, Cary, NC, USA).

3. RESULTS

3.1. Patient characteristics

Of the 140 women with refractory BPS/IC enrolled in this study, 3 (2.1%) dropped out of treatment due to personal reasons and their data were excluded. Of the remaining 137 (97.9%) patients who had completed the standard protocol of a 6-month treatment, no side effect was remarkable. Patient characteristics are listed in Table 1. Their mean ages were 47.6 ± 27.5 years, and durations of symptoms were 4.9 ± 0.4 years. Their recorded functional bladder capacity in bladder diary was 223.2 ± 93.4 mL (20–420 mL). Cystoscopy with hydrodistention disclosed typical signs of mucosal glomerulations in all patients, with 72.6% of them showing advanced grades (II and III) of glomerulations, and 6.6% Hunner's ulcers.

3.2. Therapeutic results

Responses to therapy were evaluated by comparing scores between pretreatment and posttreatment based on pain VAS, ICSI, ICPI, and PISQ-12 assessments. Changes in symptoms from the baseline to each visit are listed in Table 2. Statistically

Table 1

Characteristics of 137 women with treatment refractory interstitial cystitis who underwent intravesical therapy with a hyaluronic acid solution

Patient characteristics	Value	Range
General data		
Mean age (y)	47.6 ± 27.5	(24–77)
Mean symptomatic years	4.9 ± 0.4	(0.5–20)
Mean functional bladder capacity (mL)	223.18 ± 93.36	(20–420)
Mean voided volume on uroflometry (mL)	234.6 ± 99.6	(77–412)
Mean residual urine amount on uroflometry (mL)	33.6 ± 56.6	(0–310)
Cystoscopic findings with hydrodistention		
Mean anesthetic bladder capacity (mL)	467.1 ± 70.1	(250–900)
% with advanced (grade II&III) glomerulations	72.6	(98/135)
% with Hunner's ulcers	6.6	(9/137)

Table 2

Changes of symptoms in 137 women with refractory interstitial cystitis/bladder pain syndrome after intravesical therapy with a hyaluronic acid solution

	Baseline		1 m		6 m		*p*	*p*	*p*[a]
	Mean	SD	Mean	SD	Mean	SD	B–1 mo	B–6 mo	1—6 mo
GRA	…		1.30	±0.99	1.68	±0.88	<0.001	<0.001	<0.001
ICSI	13.69	±3.84	10.60	±4.31	9.16	±3.84	<0.001	<0.001	<0.001
ICPI	12.79	±2.73	10.76	±3.59	9.64	±3.79	<0.001	<0.001	<0.001
QoL index	26.48	±6.12	21.44	±7.47	18.79	±7.26	<0.001	<0.001	<0.001
PISQ-12	26.51	±1.05	28.57	±1.07	28.90	±1.12	0.012	0.015	1.000
VAS	5.86	±2.98	4.65	±2.70	3.81	±2.17	<0.001	<0.001	<0.001
FBC (mL)	223.18	±93.36	229.27	±79.18	257.84	±90.07	0.590	<0.001	<0.001
Voided volume (mL)	238.42	±82.73	238.56	±100.78	249.64	±126.41	1.000	1.000	0.593
PVR (mL)	30.17	±41.07	27.16	±25.80	31.33	±37.59	1.000	1.000	1.000

FBC = functional bladder capacity; GRA = global response assessment; ICSI = interstitial cystitis symptom index; ICPI = interstitial cystitis problem index; PVR = postvoid residual volume; QoL index = ICSI + ICPI; PISQ-12 = Short form of the pelvic organ prolapse/urinary incontinence sexual function questionnaire; VAS = visual analog scale of pain.[a]Repeated measure ANOVA.

significant ($p < 0.001$) improvements in both Pain-VAS and the ICSI & ICPI scores were detected soon after the initial 4 weekly instillations. Further significant improvements ($p < 0.001$) were found at the end of the 6-month treatment period. In contrast to the prompted and progressive symptomatic improvements, no notable improvement of functional outcome measures was noted until a significant increment in functional bladder capacity of 34.6 mL ($p < 0.001$) was noted after the 6-month therapy (baseline: 223.3 mL, 6 months: 257.8 mL).

Furthermore, we found 39.4% (n = 54) of our patients reported moderate/marked (+2~+3) improvements of overall bladder conditions on GRA after the initial 4-week, and similarly 59.9% (n = 82) after the 6-month treatment (Fig. 1). This indicated that 20.5% (28/137) of our patients with no early response (nonresponders) but 6 months later became responders. Finding is consistent therapy could switch nonresponders to responders over longer period of time. Nearly 40% of patients, however, were not very satisfied with HA instillation therapy.

3.3. Outcome associations

The comparison of patient characteristics between treatment responders and nonresponders at 6 months is shown in Table 3. No statistically significant difference was found in the various parameters except a greater baseline functional bladder capacity was noted in treatment responders (responder 208.1 vs nonresponders 172.3 mL, $p = 0.049$). Further GEE analysis showed that the baseline pain-VAS scores were positively correlated with treatment responses on GRA (OR: 1.164) after adjusting for confounding factors. Results suggested that patients with larger functional bladder capacity and pain-VAS scores at baseline had benefited more from the HA instillation therapy. Notably, we found no significant association between treatment outcomes and cystoscopic findings (ie, glomerulation grading, Hunner's ulcers, and anesthetic bladder capacity).

Overall, 67.9% of our patients reported treatment outcome consistent across follow-ups, with 34.3% of patients being consistent nonresponders and 33.6% being consistent responders (Table 4). Further statistical analysis (McNemar test) suggested the initial treatment responses optimally ($p < 0.001$) predicted the later treatment outcomes.

4. DISCUSSION

Our principal finding is that intravesical HA therapy suppressed pain and symptomatic scores in patients with refractory BPS/IC within the first month of treatment. The effects strengthened with continued monthly therapy. Patients who started with larger functional bladder capacities and with more serious bladder pain symptoms were more likely to gain benefits from this therapy.

A standard protocol of 6-month intravesical HA therapy was given to our patients for treatment of IC refractory to conventional therapy. Nearly, all (97.9%) patients went through the treatment uneventfully without notable adverse events, indicating good tolerability and safety profile of this treatment. HA, a glycosaminoglycan widely present in the bladder mucosa, is used to treat BPS/IC conditions refractory to conventional therapy. HA is commercially available as Cystistat (Teva UK Limited); it comes in a 40 mg/50 mL dose solution. The initial study by Riedl et al[6] on the efficacy of HA as the first-line

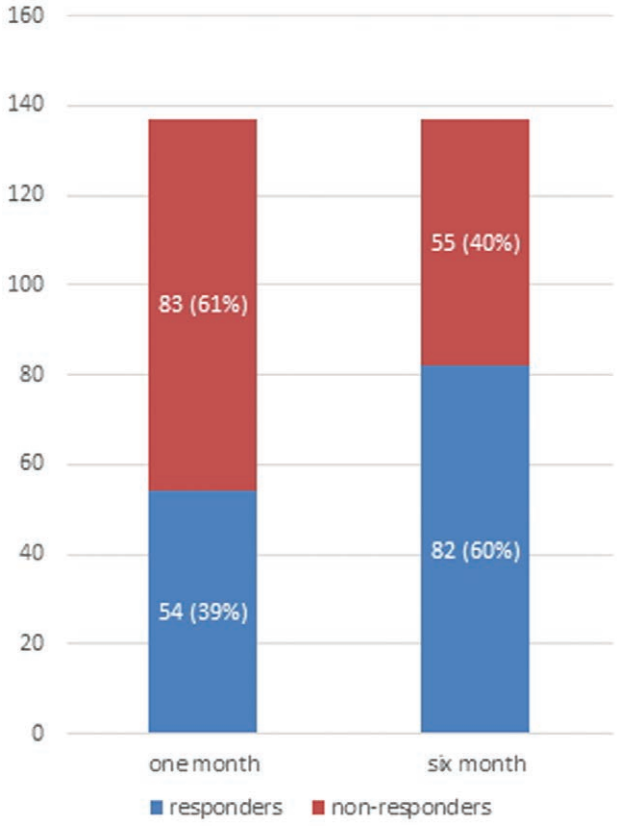

Fig. 1 Treatment responses according to GRA scores at 1- and 6- month's follow-ups. GRA = global response assessment.

Table 3

Comparison of patient characteristics between responders and nonresponders according to GRA scores after 6 months intravesical HA therapy

	Nonresponder (n = 55)		Responder (n = 82)		
	Mean	SD	Mean	SD	*p*
Age	46.13	±12.43	48.80	±11.13	0.189
Duration, y	4.26	±4.38	5.28	±5.51	0.243
Glomerulation[a]					0.842
1	14	(25.5%)	23	(28.0%)	
2	13	(23.6%)	16	(19.5%)	
3	28	(50.9%)	41	(50.0%)	
Ulcer[a]					1.000
0	51	(92.7%)	77	(93.9%)	
1	4	(7.3%)	5	(6.1%)	
ICSI	13.70	±3.60	13.71	±3.97	0.981
ICPI	12.77	±2.94	12.98	±2.60	0.665
QoL index	26.48	±6.08	26.68	±6.05	0.855
VAS	5.55	±3.04	6.19	±2.83	0.215
FBC	172.31	±102.69	208.06	±101.69	0.049*
Voided volume	230.98	±87.68	236.39	±76.86	0.727
Cystoscopic capacity	456.60	±136.44	450.80	±103.84	0.785

Independent t-test. FBC = functional bladder capacity; GRA = global response assessment; ICSI = interstitial cystitis symptom index; ICPI = interstitial cystitis problem index; QoL index = ICSI + ICPI; VAS = visual analog scale of pain.[a]Chi-square test. *$p < 0.05$.

Table 4

Treatment responses according to GRA scores at 1- and 6-month follow-ups

	GRA 1m (early)			
	Nonresponder	Responder	Total	*p*
GRA 6m (late)				<0.001[a]
Nonresponder	47	8	55	
Responder	36	46	82	
Total	83	54	137	

GRA = global response assessment.[a]McNemar test.

therapy involved 126 patients. Weekly instillations of HA were given until symptoms completely disappeared. They had an average 12.2 instillations resulting in 85% of patients reporting symptomatic improvements (≥2 VAS units). Later uncontrolled studies used 40 mg/50 mL HA weekly instillations for 4–6 weeks and then maintained on monthly doses.[16–19] Symptom evaluation was typically performed on week 12 in these studies.[19] Around 60%–80% symptomatic responses were reported 6 months after treatment. While the short-term efficacy of intravesical hyaluronan for BPS/IC has been demonstrated, little data are available regarding the time duration required to observe the therapeutic effects. Kim et al[20] also applied a study protocol of 4 weekly instillations. They reported after 4 weeks, VAS pain scores were down by –2.5 points ($p < 0.001$). The PUF-total score (–3.8, $p < 0.001$), ICSI (–2.3, $p < 0.001$), and ICPI (–2.7, $p < 0.001$) also showed significant improvements. Nonetheless, no definitive evidence-based protocol is available for the best HA instillation treatment.[21]

In this study, we found as early as 1 month after therapy (ie, 4 weekly instillations), scores of ICSI, ICPI, and pain VAS all improving significantly (specifically, ICSI and ICPI scores dropped 2–3 points, and VAS pain scores dropped 1.2 points). With continued monthly instillation therapy, all scores further improved though at slower rates. Our results showed that frequent HA instillations are beneficial in relieving acute symptoms, which is consistent with the report by Lai et al[5] in 2013 and Lee et al[22] in 2015. In their study, most patients reported symptomatic improvements during the first month of treatment, and then the improvements gradually subsided later during the maintenance period. The cause for such temporal changes may be due to the earlier direct protection effect of HA on damaged urothelium and hence relieving bladder symptoms more efficiently.[21]

Intravesical HA appeared less effective to improve bladder capacity. Our study found no changes in bladder capacity 1 month after therapy. But with monthly instillations continued on monthly basis, we found an average increase of 34 mL in their functional bladder capacities (baseline: 223.3 mL, 6 months: 257.8 mL). This finding is consistent with our previous report on patients with refractory BPS/IC, and that intravesical HA is more effective in pain relief than reducing the bladder storage symptoms.[23] Other investigators also reported similar findings.[9,24] Other possible causes of discrepancy in results are differences in the underling multifactorial etiology of BPS/IC,[24] and detrusor fibrosis/bladder shrinkage might have occurred after progressive inflammation of BPS/IC. Under those conditions, intravesical therapy may be less effective.[9,25] Therefore, to improve bladder storage function in these patients, one needs to wait for longer time and see. Combined therapy with long-term bladder training, behavior therapy, or other medical treatments is also beneficial.

Close to 40% of patients reported not feeling very satisfied with the HA instillation therapy. This proportion of dis-satisfaction is slightly higher than those reported in the literature,[6–12] except is consistent with Kim et al's study in 2014.[20] Kim et al explained that their similar discrepancy with the literature is probably because the selection criterion of their patients is those refractory to conventional therapy, a selection criterion that is the same as ours. Compared with the data from our previous study,[26] where patients with newly diagnosed BPS/IC were enrolled, this cohort was comparatively older (averaged 47.6 vs 38.8 years), with a longer symptomatic duration (4.9 vs 3.0 years), and a smaller anesthetic bladder capacity (467.1 vs 613.2 mL) (Table 1).

We found nearly 70% patients (34.3% consistent nonresponders, and 33.6% consistent responders) reported consistent treatment outcomes at both the early and late follow-ups. In other words, we can roughly estimate the final therapeutic effect of HA after intensive weekly therapy by 1 month. This report is useful for counseling with patients before and during HA therapy. This point has not been mentioned in other studies before.

Our analysis also suggested those who had suffered from more pain initially (higher baseline pain-VAS), tended to experience more dramatic impact of the HA therapy. In the contrary, patients with reduced functional bladder capacity tended to have an unsatisfactory treatment. The above findings are once again similar with our previous study.[23] Bladder instillation of HA is thought to provide a direct protection on damaged urothelium from BPS/IC and relived pain sufficiently. But in patients with characteristics suggesting a reduced bladder capacity, bladder fibrosis is always irreversible. Such chronic bladder inflammation could not be resolved by targeting on GAG supplementation only. That is our hypothesis why bladder capacity had influence on the HA instillation effect.

However, cystoscopic findings, such as glomerulation grades, Hunner's ulcers, or bladder capacity, were unrelated to the efficacy of HA instillations. This finding is consistent with another ICDB study.[27] That study concluded that neither findings of bloody irrigating fluid nor glomerulations strongly correlate with IC symptoms. In the literature, several studies of benefit from HA instillation to recurrent lower urinary tract symptoms caused by BPS/IC had been reported,[4–7,18–22] but limited

correlation between the symptoms presentation and bladder mucosa damage was found. Further designed study with larger database would be needed.

One limitation of this study is that first we did not have a placebo arm for comparison, and the results of intravesical HA therapy may be confounded by the therapeutic effect of bladder hydrodistention. However, we argue that the confounding effect, if any, would be minimal, because we used a short rather than prolonged hydrodistention at intervals of at least 4 weeks before subsequent therapy. The second limitation is the 6-month treatment is still relatively short term. However, the aim of this study was mainly to evaluate the treatment response, not the long-term efficacy. Patients with acute and severe symptoms of this disease should therefore start HA instillation with weekly instillations to achieve greater symptomatic relief.

In conclusion, intravesical therapy using HA solution is effective and safe for refractory BPS/IC, especially when applied at a frequent instillation interval. Soon after 4 weekly instillations, pain and ICSI/ICPI significantly improved, with further improvement at the end of 6 months after continued treatment. Patients with larger functional bladder capacity and severe bladder pain symptoms at baseline benefit more from the HA instillation therapy. Early treatment response can predict later response in nearly 70% of patients.

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