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To cite this article: Ray Hachem, Souha Kanj, Nelson Hamerschlak, Hala Saad, Fernanda Ferraz Assir, Nobuyoshi Mori, Ying Jiang, Fady Ghaly, Anne Marie Chaftari & Issam I Raad (2018) International experience with minocycline, EDTA and ethanol lock for salvaging of central line associated bloodstream infections, *Expert Review of Medical Devices*, 15:6, 461-466, DOI: [10.1080/17434440.2018.1483237](https://doi.org/10.1080/17434440.2018.1483237)

To link to this article: <https://doi.org/10.1080/17434440.2018.1483237>



Published online: 21 Jun 2018.



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ORIGINAL RESEARCH



International experience with minocycline, EDTA and ethanol lock for salvaging of central line associated bloodstream infections

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ABSTRACT

Background: The use of long-term central venous catheters (CVCs) could lead to serious bloodstream infections. Removal of the infected CVC and reinsertion of a new CVC are not always feasible and alternative lock therapy may be considered. We conducted a multicenter trial to assess the efficacy and safety of the lock therapy.

Methods: Between October 2013 and August 2014, we prospectively enrolled 20 patients with catheter-related bloodstream infections (CRBSIs) or central line-associated bloodstream infections (CLABSIs) in our sister institutions in three countries including Brazil, Lebanon, and Japan. The 20 patients who received M-EDTA-EtOH lock therapy were compared to 24 control patients who had their CVCs removed and a new CVC inserted.

Results: Both groups had comparable clinical characteristics. In the lock therapy group, 95% of the patients had microbiological eradication within 96 h after starting lock therapy versus 83% of the patients in the control group ($p = .36$). In the lock group, the CVC was salvaged and retained for a median of 21 days (range 7–51) from the onset of bacteremia.

Conclusion: Our study suggests that M-EDTA-EtOH lock therapy may be an effective intervention to salvage long-term CVCs in the setting of CLABSI/CRBSI and hemodialysis cancer patients with limited vascular access.

ARTICLE HISTORY

Received 23 February 2018
Accepted 29 May 2018

KEYWORDS

EDTA; ethanol lock; central catheters; central line associated; bloodstream infections; minocycline

1. Introduction

Central vascular catheters (CVCs) are essential in the management of patients with cancer, critically ill patients or those undergoing hemodialysis. Unfortunately, the use of CVC is sometimes associated with serious bloodstream infections. Changing these infected catheters is difficult in certain cases and associated with increased incurred cost. For long-term CVCs (mostly cuffed/tunneled CVCs or ports with dwell time of more than 30 days), the lumen of the catheter is the major source of colonization and subsequent bacteremia [1]. In a prospective study involving 359 indwelling silicone CVCs, the internal surface of the catheter lumen was found to be the predominant source of biofilm colonization. Hence, the guideline for the management of catheter infections [2] recommended antimicrobial lock therapy (ALT) as an intervention that may eradicate organisms in biofilm colonizing the lumen of the long-term CVC resulting in the salvage of the vascular access site.

Clinical data suggest that ALT may play a role in improving the management of central line-associated bloodstream infections (CLABSIs) [3–11]. The use of an ALT consists of filling the lumen of the catheter with 0.8-1 mL of an antimicrobial solution at a concentration 100–1000-fold higher than the

minimal inhibitory concentration of the antibiotic to the common microbial pathogens. The lock is instilled and dwells in the lumen of the CVC for a period of time while the catheter is not in use [5,12]. This along with the administration of systemic antibiotics would theoretically allow salvaging of the CVC and the vascular access site [13]. Moreover, vancomycin alone or in combination with heparin has been the most commonly used ALT solution, and was associated with remarkable failure in treating CLABSI caused by *Staphylococcus aureus* [6,13]. This might be related to the fact that glycopeptide antimicrobials, such as vancomycin, have a limited activity against slime-producing microbial organisms embedded in biofilm on a catheter surface [14–16]. *In vitro* animal and clinical studies conducted by our group showed that an ALT consisting of a tetracycline antibiotic (such as minocycline) and a chelator (such as EDTA) may eradicate microbial organisms embedded in biofilm on a catheter surface and, hence, enable treatment of CLABSI while retaining the infected catheter *in situ* [9,14–18].

Based on our prior studies, we showed that adding ethanol to this ALT (minocycline + EDTA) combination enhances its activity and results in an even more rapid eradication of organisms in biofilm [19]. Most of the clinical data are limited [3–9]. A recent open-label pilot study conducted at our

institution showed that a lock solution consisting of a triple combination of 1 mg/mL of minocycline, 30 mg/mL of EDTA, and 25% of ethanol (M-EDTA-EtOH) lock was safe and effective in salvaging the vascular access in patients with CLABSI [20]. To investigate whether this triple combination will be equally effective in the less sophisticated settings outside the USA, we conducted a multicenter phase II study using the same triple combination in three international sister institutions (Brazil, Lebanon, and Japan) to assess the feasibility and efficacy of the M-EDTA-EtOH lock in an international multicenter trial. The American University of Beirut is a teaching tertiary care center functioning as a referral center at the national and regional levels – it has 386 beds, located in Beirut, Lebanon; The Hospital Israelita Albert Einstein is a general hospital with 650 beds located in São Paulo, Brazil; St. Luke's International Hospital is a general and teaching hospital with 540 beds, located in Tokyo, Japan.

2. Patient and methods

This is a prospective open-label multicenter lock therapy for salvaging of central catheters in the setting of CLABSIs. Between October 2013 and August 2014, we enrolled 44 patients with catheter-related bloodstream infections (CRBSIs) or CLABSI in three of our sister institutions in three countries including Brazil, Lebanon, and Japan. In total, we enrolled 20 patients who received M-EDTA-EtOH lock therapy. They were selected based on the inclusion criteria listed below. Those were matched with 24 control patients based on the following criteria: (1) underlying disease, (2) neutropenia, and (3) type of organisms. All the control patients had CLABSI or CRBSI, and had their CVC removed and a new CVC inserted in a different vascular access site.

Eligible patients were aged ≥ 18 years, with indwelling CVC that had been in place for at least 14 days, with documented CLABSI or CRBSI in accordance with the definition by the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America (IDSA) [2].

Patients were ineligible if they had any of the following: severe sepsis, septic shock, prosthetic valve; signs of metastatic deep-seated infection such as osteomyelitis, endocarditis, or septic thrombosis; tunnel or catheter exit site infection or infusion port pocket abscess as manifested by purulence at the exit site or inflammation with erythema >1 cm in diameter. Patients could only participate once in this trial. Each catheter lumen was filled with a volume of 0.8–1 mL of M-EDTA-EtOH-lock solution for 2 h administered once daily for a total of seven doses.

Patients were monitored during treatment and followed for 1 month after they received the last dose of lock or had their CVC removed. We monitored the patients for the development of infectious complications including septic thrombophlebitis, hemodynamic instability following lock installation regarding hemodynamic instability. Patients were assessed as follow. Vital signs and labs monitoring were done daily during the lock therapy and once weekly up to 1 month post lock therapy. We also evaluated the patients for deep-seated infection, relapse, the occurrence of mechanical complications

including failure of CVC insertion and CVC misplacement, and any adverse events leading to the discontinuation of the catheters.

The control group was identified by retrospectively screening the microbiology lab data and the infection control surveillance database at each of the study center during the same period of enrollment of the prospective open-label arm. Patients of this control group were matched with the cases in a 2:1 ratio. However, due to lack of finding a control for each case, we decided to continue with 1:1 ratio. The matching criteria were based on similar underlying disease (hematologic malignancy vs. solid tumor), type of organism, and neutropenic status.

We designed our study to test this lock therapy in the real-world setting in patients with CLABSI or CRBSI. Out of the 20 patients enrolled, 6 patients were diagnosed with CRBSI and 14 patients with CLABSI. It is well known that CRBSI is a more accurate and specific diagnosis that relies on quantitative BC and DTP, and it will be ideal if the study can be done only in patient with CRBSI. However, the CDC definition may overestimate the CVC as being the source particularly in patients with mucosal barrier injury. This is why we relied on CRBSI definition for patients with neutropenia to avoid over treating patients who do not have a real-line-related infection. Regarding the CLABSI definition this was only applied in non-neutropenic patients who did not have a MBI. Those patients with CLABSI are likely to have a line-related infection in the absence of any other source, and they cannot be ignored, and should be treated as well.

Furthermore, it would be ideal to compare our antimicrobial lock to a standard of care lock, but until today the conventional standard of care in the management of line-related infection is removal of the infected CVC and replacement of a new catheter at a different vascular site [2]. Moreover, there is no standard of care lock approved by the Food and Drug Administration (FDA). In addition, there are insufficient data and poor evidence-based recommendation for a standard of care lock particularly for staph aureus and Gram negative. Whereas the removal of the catheter is given a higher grade of recommendation (All), the lock therapy, with the dwell time, is given a much lower level of recommendation (BII) at best. In addition, the selection of antibiotic, its dose, and the dwell time of lock therapy are not well standardized. Current lock therapy may require at least 12 h of dwell time which could not be practical in the management of patients who need their line for the administration of chemotherapy or others essential systemic and supportive therapy. From our experience, locking the line for more than 2hrs may not be always feasible in cancer patients. Hence, our study design is to lock the line for only 2 h per day. On the other hand, if we compared our lock to a control lock that dwell in the catheter for more than 12 h will not be an appropriate design.

This study was approved by three sister institutional review boards and all patients had to sign informed consent at their institution which includes the American University of Beirut,

Lebanon; Albert Einstein, Sao Paulo, Brazil; and the St. Lukes International Hospital, Tokyo, Japan.

3. Definitions

CLABSI was defined according to CDC criteria having at least one positive blood culture with a recognized pathogen or two positive blood cultures with a common skin contaminant in the presence of clinical manifestations of infection in a patient who has no apparent source of the bacteremia other than the CVC. CRBSI was defined as per IDSA criteria, as a bloodstream infection where the blood culture drawn from the CVC turned positive at least 2 h earlier than the blood culture simultaneously drawn from the peripheral site [2], or a paired blood culture drawn simultaneously through the CVC and peripheral vein, revealing threefold or greater number of colonies from the CVC.

Neutropenia was defined as an absolute neutrophil count < 500 cells/mm³.

Microbial eradication was defined as the absence in culture of the original infecting pathogen.

4. Statistical methods

The chi-square or Fisher's exact test was used to compare categorical variables, as appropriate. The Wilcoxon rank-sum test was used to compare continuous variables. The Kaplan-Meier method was used to estimate the cumulative incidence densities of microbiological eradication for patients treated with lock therapy and for controls, and the log-rank test was used for the comparison of two groups. All tests were two-sided tests with a significance level of 0.05. The statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

5. Results

A total of 20 patients with CLABSI/CRBSI were prospectively evaluated in the three sister institutions using the M-EDTA-EtOH lock therapy to salvage the catheters. Those patients were matched with 24 control patients who had their CVCs removed and a new CVC inserted. The demographic data such as age, gender, and race were similar in both groups (Table 1). In the patients receiving lock therapy, the median age was 54 years. The majority were males (65%) and middle eastern (40%) or white (35%). With regard to the clinical data, 90% of patients who received lock therapy had cancer while 71% of control patients did ($p = .15$). The two groups had comparable clinical characteristics including diabetes (25% vs. 25%), neutropenia (30% vs. 35%), Graft-versus-host disease (GVHD) (10% vs. 5%), hemodialysis (5% vs. 17%), intensive care unit admission (55% vs. 42%), and fever (80% vs. 71%). Bacteremia was caused by Gram-negative organisms in 55% patients (including polymicrobial bacteremia) in the lock therapy group and in 38% patients in the control group ($p = .25$). This was not statistically significant, possibly due to small sample size. The most common organisms included coagulase negative staphylococci (35% vs. 29%), *Klebsiella* spp. (20% vs. 13%), and *S. aureus* (5% vs. 4%).

All the patients in both groups received similar appropriate systemic antibiotic treatment for their bacteremia. We did not find any significant difference in any type of antibiotics used (Table 2). The durations of systemic antibiotic therapy were also similar in both groups (median: 14 days vs. 15 days) ($p = .25$).

In the control patients who had their CVCs removed and a new CVC inserted due to CLABSI/CRBSI, the median length of time from the onset of bacteremia to CVC removal was 2 days (range: 0–8 days) (Table 3). Lock therapy was initiated within 48 h of the onset of bacteremia 2 days for patients. The patients were treated with a median number of seven doses of lock solution (range –four to seven doses) with each dose given on a different day.

Sixteen patients in the lock therapy group (80%) and 17 patients in the control group (71%) had fever at onset of bacteremia. Of them, 15 patients receiving lock therapy (94%) and all the 17 control patients (100%) had fever resolution within 24 h ($p = .48$). In those infected with Gram-negative organisms, the rate of fever resolution was 100% for both groups. In addition, 95% of the patients in the lock therapy group and 83% in the control group had microbiological eradication within 96 h after either starting lock therapy or CVC removal ($p = .36$). In those infected with Gram-negative organisms, 89% of patients receiving lock therapy and 67% of control patients go microbiological eradication within 96 h ($p = .58$). Similarly, there was no significant difference in cumulative incidence density of microbiological eradication between the two groups ($p = .84$) (Figure 1). The lengths of time from CVC management (lock or removal) to fever resolution (median: 3 days vs. 1 day) and to microbiological eradication (median: 2 days vs. 3 days) were both comparable between the two groups. In the lock therapy group, one patient had his CVC removed at day 7 for persistent bacteremia and considered failure. The remaining 19 patient's CVCs were salvaged and retained until no longer needed for management. Their catheters were removed as follows: 2 patients at day 10, 3 patients at day 15, 4 patients at day 21, 1 patient at day 30, 2 patients at day 36, 3 patients at day 55, and 4 patients had their catheters in place at day 160, with a median of 21 days (range 7–160) from the onset of bacteremia. In the control group, the CVC was removed after a median of 2 days in the control group (range 0–8 days, $p < .0001$). None of the patients reported any complications. Safety data including hemodynamics instability following lock with M-EDTA-EtOH, deep-seated infection, and relapse were assessed during lock and post 30 days after the end of lock therapy.

6. Discussion

This novel M-EDTA/EtOH lock therapy with a triple combination was shown to be safe and efficacious in salvaging the catheter in three different international centers. The rate of persistent infection in the lock intervention arm was minimally lower than the control arm. But overall, infectious outcome including clearance of the bacteremia without catheter replacement or dissemination of infection (deep-seated infections) was equivalent to the control arm. These findings were consistent with results from another trial conducted at one single

Table 1. Characteristics of patients who received lock solution therapy and their controls.

Characteristic	Lock solution (n = 20) N (%)	Controls(n = 24) N (%)	p-value
Age (years), median (range)	54 (23–84)	59 (21–96)	> .99
Gender, male	13 (65)	18 (75)	.47
Center			.84
Lebanon	9 (45)	10 (42)	
Brazil	9 (45)	10 (42)	
Japan	2 (10)	4 (17)	
Cancer	18 (90)	17 (71)	.15
Type of cancer			.18
Hematologic malignancy	17/18 (94)	13/17 (76)	
Solid tumor	1/18 (6)	4/17 (24)	
Neutropenia (≤ 500 cells/ mm^3)	6 (30)	8/23 (35)	.74
ICU admission during study period	11 (55)	10 (42)	.38
GVHD	2 (10)	1 (4)	.20
Hemodialysis	1 (4)	4 (17)	.36
TPN	4 (20)	6 (25)	.73
Type of CVC			.43
PICC	4 (20)	10 (42)	
Tunneled cath. surg. implanted	5 (25)	3 (13)	
Non-tunneled	7 (35)	6 (25)	
Dialysis catheter	4 (20)	4 (21)	
CRBSI	6 (30)	7 (29)	
Fever ($>38^\circ\text{C}$) at onset of bacteremia	16 (80)	17 (71)	.48
Bacterial species causing bacteremia			
Gram positive			
<i>Staphylococcus aureus</i>	1 (5)	1 (4)	
Coagulase negative Staphylococci	7 (35)	7 (29)	
<i>Streptococcus</i> spp.	1 (5)	4 (17)	
<i>Enterococcus</i> spp.	1 (5)	3 (13)	
Gram negative			
<i>E. coli</i>	1 (5)	2 (8)	
<i>E. coli</i> and <i>Streptococcus</i> spp.	1 (5)	0	
<i>Klebsiella</i> spp.	4 (20)	3 (13)	
<i>Pseudomonas aeruginosa</i>	1(5)	1 (4)	
	1 (5)	2 (8)	
<i>Rhizobium radiobacter</i>	1 (5)	0	
<i>Burkholderia cepacia</i>	1 (5)	1 (4)	

Abbreviations: GVHD: graft-versus-host disease; TPN: total parenteral nutrition; PICC: peripherally inserted central catheter.

tertiary cancer center in the USA using the same lock therapy solution. This lock therapy was demonstrated to be highly efficacious in salvaging the CVC for a median of 66 days [20]. Hence, the findings from both trials showed promising results with this lock therapy and warrant further consideration for its use as a standard of care in clinical practice.

In previous studies, we showed that the combination of minocycline and EDTA prevented catheter-related bacteremia and colonization *in vitro* as well as in clinical trials involving hemodialysis and cancer patients [5,14,16–18]. The necessary long dwell time of the EDTA-minocycline lock therapy contributed to its effectiveness, but locking the catheter for 12–24 h is not feasible for seriously ill patients especially cancer patients where the catheter is needed for infusion of various products.

In contrast, the three components (minocycline, EDTA, and ethanol) of this novel lock act in synergy to rapidly eradicate multidrug-resistant bacteria in biofilms within 15–60 min in a manner which is superior to ethanol alone [19,21].

Furthermore, the low concentrations of Ethanol, EDTA, and minocycline were selected after extensive *in vitro* testing where we validated the adequate antibacterial activity to eradicate various multidrug resistant organisms embedded in biofilm [21]. In addition the reason we used this low concentration of ethanol 25% is to avoid the toxicity from high dose while preserving its activity. A study by Slobbe et al. showed that ethanol 70% is associated with statistical significant adverse events such as facial flushing, nausea, vomiting, altered taste, and feeling of dizziness/drowsiness [10].

A randomized control trial by Slobbe et al. that compared the effectiveness of 70% ethanol lock to placebo among adult hematology patients using a dwell time of only 15 min did not find a significant reduction in the risk of endoluminal CRBSI.

There is no consensus on the appropriate dwell time of lock therapy. We therefore in this study investigated a short dwell time lock therapy for only 2 h by using the triple combination of minocycline, EDTA, and 25% of ethanol in order to achieve a total kill and successful outcome.

The results of this current trial demonstrate that locking the CVC for 2 h in 20 patients with documented CLABSI/CRBSI caused by various bacteria including Gram-positive, Gram-negative, and polymicrobial organisms resulted in the successful outcome with resolution of the infection and salvaging of the infected line. Overall, the MEDTA/EtOH lock therapy was successful in 95% of the patients in the interventional lock

Table 2. Systemic antibiotic treatment of bacteremia for patients receiving lock solution and their controls.

Systemic antibiotic treatment of the bacteremia	Lock solution(n = 20) N (%)	Controls(n = 24) N (%)	p-value
Anti-Gram positive			
Linezolid	1/11 (9)	1/15 (7)	>.99
Daptomycin	2/11 (18)	2/15 (13)	>.99
Vancomycin	9/11 (82)	13/15 (87)	>.99
Anti-Gram negative			
Cefepime or ceftazidime	4/11 (36)	5/9 (56)	.65
Meropenem or ertapenem	11/11 (100)	7/9 (78)	.19
Piperacillin/tazobactam	1/11 (9)	1/9 (11)	>.99
Duration of antibiotic therapy (days), median (range)	14 (5–21)	15 (7–35)	.25

Table 3. Clinical and microbiological responses of patients receiving lock solution and their controls.

Response	Lock solution (n = 20) N (%)	Controls (n = 24) N (%)	p-value
Fever resolution	15/16 (94)	17/17 (100)	0.48
Days between bacteremia and fever resolution, median (range)	2 (0–5)	2 (1–7)	0.93
Days between starting intervention and fever resolution, median (range)	1 (1–3)	1 (1–2)	0.24
Microbiology eradication within 96 h after intervention	19 (95)	20 (83)	0.36
For patients with microbiological eradication after starting intervention (catheter removal or lock therapy)			
Days between starting intervention and microbiology eradication, median (range)	2 (1–4)	3 (1–4)	0.85
Days between bacteremia and catheter removal or exchange, ^a median (range)	21 (7–160)	2 (0–8)	<0.0001

^a In four patients, the CVCs were still in place on last day of patient contact.

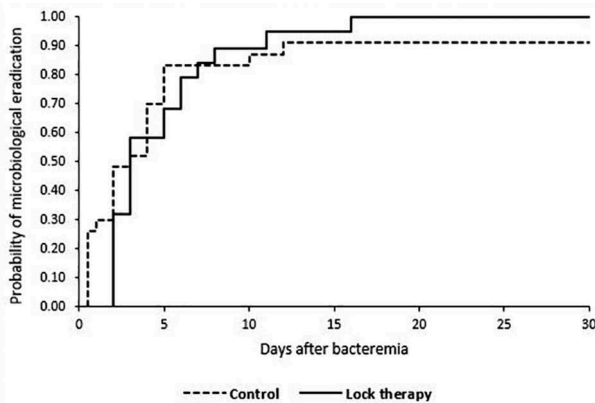


Figure 1. Estimated cumulative incidence curves of microbiological eradication for patients treated with lock therapy and controls ($p = .84$).

therapy arm versus 83% in the concurrent control CVC removal/reinsertion group.

The median length of time from the onset of bacteremia to CVC removal was significantly longer in the M-lock group (median of 21 days, range: 7–160 days) versus median of 2 days with a range 0–8 days in the control group ($p < .0001$). This salvage is very crucial in this patient population with limited vascular access and frequently associated thrombocytopenia or other coagulopathies.

Our patients received a median of seven doses of lock therapy (range four to seven doses). However, not all patients remained in the hospital until the end of therapy. Most patients were discharged home once afebrile and stable to continue their lock therapy in the outpatient setting. The duration of systemic antibiotic therapy was also similar in both groups with a median duration of 14 days. In our study, the M-lock solution was easily administered and well tolerated and there were no reported adverse events associated with the lock solution.

A decision regarding the use of antimicrobial lock solution should be driven by its broad spectrum antimicrobial activity

against organisms embedded in biofilm, availability of IV minocycline and EDTA in some countries, ease of administration, short dwell time, minimal interactions with catheter material, high tolerability with low toxicity, and cost saving. Our novel lock solution used in this study seems to fulfill all the above qualifications and may be considered as an optimal lock.

Our study had several limitations. First, this is a small sample size with only 20 patients who received lock therapy and with 24 patients in the control arm. Second, using a control group that had their CVC removed and then having that as primary end point creates a selection bias. Third, this study was intended to have a matching ratio of 2:1, but we used a ratio of 1:1, because we were not able to identify enough patients. Fourth, patients were monitored for 1 month post lock therapy. Future trials may recommend longer periods of follow-up.

7. Conclusion

In conclusion, our study suggests that M-lock therapy seems to be an effective intervention to salvage long-term CVCs in the setting of CLABSI/CRBSI in cancer and dialysis patients with limited vascular access. Further investigations to validate these findings and assess the safety of M-lock in a larger phase III randomized clinical trial are warranted.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

Ray Hachem – Designed, wrote and supervised the paper.
 Nelson Hamerschlak – Supervised, and wrote the paper.
 Fernanda Ferraz Assir – Supervised and helped in writing the paper.
 Ying Jiang – Collected and analysed data for the paper.
 Anne Marie Chaftari – Helped in writing the paper.
 Souha Kanj – Helped in writing the paper and supervised the trial conduct.
 Hala Saad – Collected data and engaged in patient follow-up.
 Nobuyoshi Mori – Supervised and helped in writing the paper.
 Fady Ghaly – Collected data.
 Issam I. Raad – Designed and wrote the paper.

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