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Major Article

Active surveillance at the time of hospital admission for multidrug-resistant microorganisms among patients who had recently been hospitalized at health care facilities

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Background: This study aimed to investigate the epidemiology of multidrug-resistant microorganism (MDRO) carriage at hospital admission and to identify risk factors for MDRO influx into hospital settings.
Methods: This cohort study was conducted at a 1,051-bed university-affiliated hospital in the Republic of Korea between July 1 and December 31, 2017. Active surveillance for MDRO carriage was performed within 48 hours of hospitalization in all adult patients who had prior hospitalization within the preceding 3 months.
Results: During the study, 575 patients were admitted with a hospitalization history within 3 months. Active surveillance at hospital admission was performed in 192 eligible patients. Thirty-three (17.2%) patients with MDRO carriage were identified from active surveillance. In the multivariate logistic regression analysis, prior exposure to antibiotics within 90 days, hospitalization for ≥60 days before admission, cognitive dysfunction, percutaneous drainage, and underlying pulmonary diseases were identified as independent risk factors for MDRO influx.
Conclusions: Our findings suggest a significant prevalence of MDRO acquisition at acute care hospital admission in patients who had been recently hospitalized. To control the spread of MDRO, collaborations among health care institutions and targeted screening at hospital admission according to patient risk factors are warranted.

Multidrug-resistant microorganisms (MDROs) have posed a major threat to public health worldwide. Infections caused by MDROs account for higher morbidity and mortality rates, and thus higher health care costs compared with infections caused by antimicrobial-susceptible bacteria.[1-3] Although MDROs historically have been considered to be primarily nosocomial pathogens, these pathogens are now prevalent in long-term care facilities and have spread into the community, resulting in an influx of patients who have MDROs isolated at hospital admission.[4-9]

The influx of MDROs into the hospital setting increases colonization pressure and the risk for spread of MDROs. Namely, the new emergence of MDRO carrier status in an individual patient can happen through patient-to-patient transmission of MDROs, as well as through de novo acquisition of antimicrobial resistance during patient treatment.

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For the prevention, transmission control, and eradication of MDROs, an infection prevention and control program consist of multiple interventions and strategies. In particular, the containment strategies of MDRO spread should include an early identification of MDRO carriage with other control efforts as a basic set of MDRO infection control measures.[10] There is considerable evidence to support the use of active surveillance cultures for high-risk patients and during outbreaks of infection and colonization caused by MDROs.[11,12] However, the prevalence of MDRO acquisition and status of personnel and infrastructure resources for infection prevention and control programs may affect the clinical- and cost-effectiveness of active surveillance screening.

Recently, the improvement of lifestyle and medical care has led to a significant increase in life expectancy, and therefore an increase in the proportion of the elderly and an increase in populations with chronically complex conditions. These patients have an increased risk for acquisition of MDROs because of age or medical condition-associated morbidities, repeated admission, exposure to recurrent antibiotic treatment, and frequent referral to and from acute care hospitals.[13-15] These patients repeatedly intermingle among health care institutions and can act as reservoirs of MDRO spread.

However, previous studies on the prevalence and risk factors of MDRO influx into a tertiary hospital in patients with health care hospitalization are few.[6-9,16] The purpose of this study was to assess the prevalence of MDROs at hospital admission and to investigate the risk factors for MDRO influx into the hospital setting among patients who had been hospitalized within the preceding 3 months.

METHODS

Study design and patients

A cohort study was conducted at a 1,051-bed university-affiliated hospital in the Republic of Korea, between July 1 and December 31, 2017. Active surveillance cultures for MDROs were obtained within 48 hours of hospital admission from all patients who had been admitted at health care institutions for ≥7 days during the preceding 3 months. MDROs included methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and carbapenem-resistant *Acinetobacter baumannii* (CRAB); carbapenem-resistant Enterobacteriaceae (CRE) was also considered an MDRO, because of its prevalence and increasing infection rate.[17] Patients colonized with CRE or VRE were placed under contact precautions, placed in isolation, and underwent follow-up surveillance culture after hospital admission; those colonized with MRSA or CRAB were not.

A single patient could have more than 1 type of MDRO during the study period and the data for this patient was counted separately for each MDRO isolation. For patients with multiple isolation of the same MDRO during the study period, only the first isolation was analyzed. In the analysis of predictors associated with MDRO acquisition at hospital admission, patients with multiple episodes of different MDROs were included once.

Variables

Electronic medical records were reviewed to extract relevant demographic and clinical information, including age, sex, admission source (long-term care facility or acute care hospital), length of hospital stay within the last 90 days, Eastern Cooperative Oncology Group (ECOG) Performance Status,[18] comorbidities, Charlson Comorbidity Index,[19] presence of pressure ulcers, percutaneous drainage, microbiological data, 30-day hospital mortality and exposure to medical procedures within the last 90 days, surgery, or prior antibiotic exposure within the last 90 days.

Microbiological evaluation

For screening MRSA, nasal swabs were inoculated directly onto ChromID MRSA-Select agar plates (bioMérieux, Marcy-l'Étoile, France) and incubated overnight at 35°C. For screening VRE, rectal swabs were plated directly onto ChromID VRE-Select agar plates (bioMérieux). For screening CRAB, nasopharyngeal swabs were inoculated onto nonselective Trypticase soy agar with 5% sheep blood (TSA II; BD Diagnostics, Sparks, MD), and the identification and antibiotic susceptibility test were performed as usual. For screening CRE, rectal swabs were plated directly onto chromID CARBA (bioMérieux) and incubated overnight at 35°C. To confirm carbapenemase production and the type of carbapenemase, CRE isolates were first tested using the modified Hodge test (Rosco Diagnostica A/S, Taastrup, Denmark), and then tested using a polymerase chain reaction assay for known carbapenemase genes (*KPC*, *VIM*, *IMP*, *NDM-1*, *GES*, and *OXA*-48) by the Xpert Carba-R assay (Cepheid, Sunnyvale, CA).

Morphologically distinct colonies were identified using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. Species identification and drug susceptibility testing of isolates were performed using Microscan WalkAway 96 plus system (Siemens Healthcare Diagnostics, Berkeley, CA) based on standard criteria as defined by the Clinical and Laboratory Standards Institute.[20] Although our study focused on actively identifying patients colonized with MDROs through surveillance cultures, data on clinical specimens were also collected and analyzed.

Statistical analysis

For descriptive purposes, medians, interquartile ranges, and frequencies were calculated as appropriate. The Pearson's χ^2 test or the Fisher exact test were used for univariate analyses of categorical variables. A 2-sample Student t test or the Mann-Whitney U test was used to analyze normally or non-normally distributed continuous variables, respectively.

To identify predictors associated with MDRO acquisition at hospital admission, multivariable logistic regression analysis using backward stepwise variable selection based on the Wald statistic was used. In multivariable logistic regression analysis, clinically relevant variables with a P value of <.10 as predictors of MDRO acquisition in the univariate analyses were included as candidate variables. The models were evaluated using the Hosmer-Lemeshow goodness-of-fit test. To evaluate the performance of the final logistic regression model, the predictive accuracy was calculated using leave-one-out cross-validation (LOOCV).

IBM SPSS Statistics version 20.0 (IBM, Armonk, NY) and SAS 9.4 (SAS Institute, Cary, NC) were used for all statistical analyses. Two-sided P values <.05 were considered statistically significant.

Ethics

The institutional review board of the Korea University Anam Hospital approved the protocol and waived the need for informed consent, because the data were obtained in a subset of hospitalized patients through a routine hospital surveillance program for infection control purposes (institutional review board registration no. 2019AN0052).

RESULTS

Patient characteristics

During the study period, 575 cases out of 22,606 admissions had recently been hospitalized at health care institutions within the preceding 90 days. Of these, 55 patients were <18 years old, 236 patients

Table 1
Comparison of demographic and clinical characteristics between the patients with MDROs and those without MDROs at hospital admission

Variables	Total (N = 192)	MDRO carriers (n = 33)	MDRO noncarriers (n = 159)	*P* value
Male, n (%)	77 (40.1)	19 (57.6)	58 (36.5)	.024*
Age, median (IQR)	68 (54-79)	75 (55-80)	67 (54-78)	.181
Hospitalization days before admission, median (IQR)	9 (5-30)	14 (7-82)	8 (5-21)	.011
Hospitalization days before admission ≥60 days, n (%)	31 (16.1)	13 (39.4)	18 (11.3)	<.001*
Admission route, n (%)				.036*
Emergency room	102 (53.1)	23 (69.7)	79 (49.7)	
Outpatient clinic	90 (46.9)	10 (30.3)	80 (50.3)	
Previous admission, n (%)				
Acute care hospital	158 (82.3)	22 (66.7)	136 (85.5)	.010*
Long-term care hospital	28 (14.6)	10 (30.3)	18 (11.3)	.012*
Nursing home	6 (3.1)	1 (3.0)	5 (3.1)	1.000
Admission type, n (%)				
Transfer	37 (19.3)	9 (27.3)	28 (17.6)	.200
New admission	155 (80.7)	24 (72.7)	131 (82.4)	
Comorbidity, n (%)				
Cardiovascular diseases	114 (59.4)	23 (69.7)	91 (57.2)	.185
Neurologic diseases	56 (29.2)	15 (45.5)	41 (25.8)	.024*
Malignant diseases	15 (7.8)	4 (12.1)	11 (6.9)	.296
Trauma	61 (31.8)	7 (21.2)	54 (34.0)	.152
Renal diseases	14 (7.3)	4 (12.1)	10 (6.3)	.267
Hepatic diseases	8 (4.2)	0	8 (5.0)	.355
Pulmonary diseases	19 (9.9)	9 (27.3)	10 (6.3)	.001*
Connective tissue diseases	1 (0.5)	0	1 (0.6)	1.000
Metabolic diseases	65 (33.9)	14 (42.4)	51 (32.1)	.253
Charlson index score, median (IQR)	3 (2-5)	5 (3-7)	3 (2-4)	<.001*
Predisposing factors				
Bed-ridden state, n (%)	22 (11.5)	8 (24.2)	14 (8.8)	.030*
Cognitive dysfunction, n (%)	11 (5.7)	6 (18.2)	5 (3.1)	.004*
ECOG Performance Status, median (IQR)	0 (0-1)	1 (0-3)	0 (0-1)	.001
Recent surgery, n (%)	30 (15.6)	2 (6.1)	28 (17.6)	.096*
Prior antibiotic prescription, n (%)	114 (59.4)	26 (78.8)	88 (55.3)	.013*
ICU care, n (%)	1 (0.5)	0	1 (0.6)	1.000
Foley catheterization, n (%)	11 (5.7)	5 (15.2)	6 (3.8)	.024*
Central venous catheterization, n (%)	1 (0.5)	1 (3.0)	0	.172
Nasogastric tube, n (%)	6 (3.1)	5 (15.2)	1 (0.6)	.001*
Percutaneous drainage, n (%)	6 (3.1)	3 (9.1)	3 (1.9)	.064*
Tracheostomy, n (%)	3 (1.6)	3 (9.1)	0	.005*
Hemodialysis, n (%)	4 (2.1)	1 (3.0)	3 (1.9)	.533
Sore sites, n (%)	12 (6.2)	5 (15.2)	7 (4.4)	.036*
30-day in-hospital mortality, n (%)	3 (1.6)	1 (3.0)	2 (1.3)	.434

ECOG, Eastern Cooperative Oncology Group; *ICU*, intensive care unit; *IQR*, interquartile range; *MDRO*, multidrug-resistant microorganisms.
*Variables were included in the multivariable logistic regression analysis.

refused active surveillance cultures because of the cost burden, 41 patients did not undergo the examination due to hospital stay within 3 days, and 51 patients rejected the tests because of the inconvenience of the sampling process. Finally, a total of 192 patients were included in our analysis. The demographic and clinical characteristics of the study subjects are summarized in Table 1.

MDRO isolates recovered at hospital admission

In total, 33 patients (17.2%) were colonized with 1 or more of MRSA, VRE, CRAB, or CRE. Of these, 4 patients harbored >1 microorganism: MRSA and CRAB (n = 1), MRSA and CRE (n = 1), VRE and CRE (n = 1), or MRSA, VRE, and CRAB (n = 1).

Through active surveillance culture, MRSA was detected in 19 (9.9%) patients. Of these, MRSA was isolated from the clinical specimens of 3 patients, and 2 patients received antibiotic therapy for skin and soft tissue infection and complicated intra-abdominal infection caused by MRSA. Of 10 (5.2%) patients colonized with VRE, 1 patient was known to have been colonized previously, and VRE were isolated from the clinical specimens of 4 patients during hospitalization, but no patient received antibiotic therapy for VRE infection. CRAB was isolated in 6 (3.1%) patients on active surveillance cultures; 3 patients had CRAB on clinical specimens, and 1 patient received antibiotic therapy for pneumonia caused by CRAB. Three patients (1.6%) were colonized with CRE, and 2 of 3 patients were colonized with carbapenemase-producing Enterobacteriaceae with *KPC* (n = 1) and *VIM* (n = 1) genes. No patient with infection caused by CRE required antibiotic therapy.

Risk factors for harboring MDROs at hospital admission

Table 1 shows a comparison of the demographic and clinical characteristics between the patients with MDRO acquisition and those without MDRO acquisition. The patients with MDRO acquisition had higher Charlson index scores or ECOG Performance Status and a history of more frequent hospitalization in long-term care hospitals and were more commonly admitted through the emergency room than those without MDRO acquisition. They also had more frequent underlying neurologic or pulmonary diseases and prior antibiotic prescriptions (Table 1). There was no significant difference in 30-day in-hospital mortality between the 2 groups (Table 1).

In the multivariable logistic regression analysis, hospitalization for ≥60 days before admission (odds ratio [OR], 3.55; 95% confidence interval [CI], 1.27-9.89), prior exposure to antibiotics within 90 days (OR, 3.09; 95% CI, 1.09-8.77), cognitive dysfunction (OR, 5.09; 95% CI, 1.12-23.09), percutaneous drainage (OR, 8.28; 95% CI, 1.14-60.32), and underlying pulmonary diseases (OR, 6.33; 95% CI, 2.01-20.00) were found as independent risk factors for MDRO influx (Table 2).

Table 2
Predisposing factors associated with the acquisition of multidrug-resistant microorganisms at hospital admission

Variables	Odds ratio	95% Confidential interval	*P* value
Prior antibiotic prescription (yes)	3.089	1.088-8.765	.034
Hospitalization days before admission ≥60 days	3.545	1.272-9.885	.016
Underlying pulmonary diseases (yes)	6.334	2.007-19.992	.002
Cognitive dysfunction (yes)	5.092	1.123-23.090	.035
Percutaneous drainage (yes)	8.282	1.137-60.320	.037
Male (yes)	2.221	0.910-5.418	.080
Recent surgery (no)	5.011	0.791-31.733	.087

The *P* value for the Hosmer-Lemeshow goodness-of-fit test was .384, greater than the .05 significance threshold; therefore, there was no significant evidence for lack of fit in any of the final models.

LOOCV was performed to assess the predictive accuracy of the final model. The area under the receiver operating characteristic curves for the clinical failure model were approximately 0.82 (95% CI, 0.76-0.87) and 0.77 (95% CI, 0.71-0.83) for both raw data and LOOCV. For this model, the sensitivity, specificity, positive predictive value, and negative predictive value obtained with an optimal cut-off point are described in Figure 1.

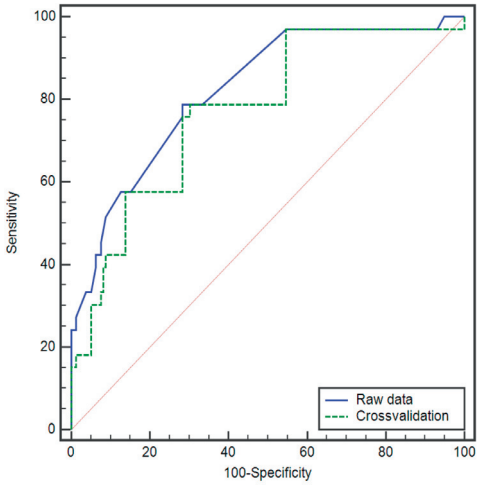
DISCUSSION

This study demonstrated the significant influx of MDROs into the health care setting from newly admitted patients who are colonized or infected with MDROs. To reduce the time that such unrecognized reservoirs might disseminate MDROs, our findings also indicated the risk factors of patients at higher risk for being colonized or infected with MDROs at the time of hospital admission. This would allow targeted screening procedures or preemptive isolation.

In our study, the prevalence of MDRO carriage identified from active surveillance at hospital admission was 17.2%: 9.9% MRSA, 5.2% VRE, 3.1% CRAB, and 1.6% CRE. These data were not significantly different from previous studies: 1.1%-10.4% MRSA, 0.3%-6.3% VRE, 4% CRAB, and 1.4% CRE.[4,6,21-23] Those colonized with MDROs at the time of hospital admission might act as Trojan horses in terms of the spread of MDROs within a hospital. In our findings, active surveillance cultures compensated for the underestimation of MDRO reservoirs from clinical cultures.

Most infection prevention and control programs in hospitals have targeted the middle component of the epidemic or endemic state during hospitalization. Now, programs should be conducted across all stages of the MDRO transmission chain, starting with the identification of patients harboring MDROs at hospital admission.[24] MRSA in Asia is common, and community-acquired MRSA in developed countries is already widely prevalent.[25-27] VRE is endemic in numerous health care institutions in Asia, Europe, and the United States.[28,29] Active surveillance programs have been achieved, decreasing the overall prevalence of VRE and the number of infections with VRE over time.[30,31] Particularly, for impeding the spread of VRE in health care institutions, several studies have already suggested the need for the early identification and pre-emptive isolation of VRE carriers at the time of hospital or intensive care unit admission.[4,21,22,32,33] Although studies are still very few, recent studies have demonstrated a substantial increase in the number of patients who harbor multidrug-resistant gram-negative bacteria at hospital admission.[8,9] Quantifying their burden would provide the fundamental data for infection control strategies to target patients at higher risk of MDRO acquisition for screening and other interventions at the time of hospital admission. Indeed, the application of infection control policy in a local context, considering individual MDRO prevalence, limited available resources, culture, and public health needs, would be important in the decision to prioritize infection control activities and the implement targeted screening strategies at the national and facility levels.[34]

Numerous studies have identified risk factors for nosocomial colonization or infection caused by individual MDROs during hospitalization: old age, underlying diseases and severity of illness, inter-institutional transfer of the patient, prolonged hospitalization, gastrointestinal surgery or transplantation, and exposure to invasive devices or antibiotics.[35] However, few studies have attempted to establish risk factors for acquisition of MDROs at hospital admission. In our study, hospitalization for ≥60 days before admission, prior exposure to antibiotics within 90 days, cognitive dysfunction, percutaneous drainage, and underlying pulmonary diseases were found as independent risk factors for MDRO



	Raw data	Cross-validation (LOOCV)
AUC (95% CI)	0.822 (0.761-0.874)	0.772 (0.706-0.830)
Cutoff value	>0.147	>0.111
Sensitivity (95% CI)	78.8 (61.1-91.0)	78.8 (61.1-91.0)
Specificity (95% CI)	71.7 (64.0-78.5)	69.8 (62.0-76.8)
PPV (95% CI)	36.6 (29.9-43.9)	35.1 (28.7-42.1)
NPV (95% CI)	94.2 (89.3-96.9)	94.1 (89.3-96.9)

AUC, area under the receiver operating characteristic curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LOOCV, leave-one-out cross validation

Fig 1. Receiver operating characteristic curve for the acquisition of multidrug-resistant microorganisms on hospital admission, obtained using the predictive probability of multivariable logistic regression model and validation results. *AUC*, area under the receiver operating characteristic curve; *CI*, confidence interval; *PPV*, positive predictive value; *NPV*, negative predictive value; *LOOCV*, leave-one-out cross-validation.

acquisition at hospital admission in patients who had recently been hospitalized at health care facilities. Various studies suggest the prolonged hospital stay variable as a risk factor for MDRO acquisition, similar to our results.[35] However, there are few studies that specify a definite period of hospitalization as a risk factor for colonization by MDROs.[36-38] Of course, this period would be influenced by other risk factors identified as important factors for MDRO acquisition.[38] Previous studies have provided similar risk factors for MDRO influx into a hospital: previous hospitalization,[4,21,22] prior exposure to antibiotics,[4,8,21,22] old age,[4,21] previous recovery from MRSA acquisition,[4] long-term hemodialysis,[4] exposure to acid-suppressive medication,[8] and transfer from a long-term care facility or hospital.[6,8,21] The risk factors during hospital stay found in previous studies were also similar to those at hospital admission identified in this study. Of note, our analysis included only patients who had been hospitalized within the past 3 months and investigated risk factors that might have occurred during the previous hospitalization.

Overall, considering these predictors, cross-transmission due to previous exposure to health care settings and the emergence of resistance from previously susceptible bacteria due to antimicrobial exposure are supposed to play a major role in the dissemination of MDROs. Therefore, they can be considered as provisional factors that can serve to stratify the risks in any future targeted screening strategies.

For the prevention and control of MDRO spread by medical institution-to-institution transfer of patients, multifaceted interventions and strategies are required. Early identification of MDROs on hospital admission through the context of active surveillance cultures should be followed by proper implementation of core infection control measures, including contact precautions, single room isolation or cohort, effective environmental cleaning, and hand hygiene. It is also essential to enhance infection prevention and control practices in small and medium-sized hospitals and to implement policies specific to these settings that can reduce MDRO transmission.

In our findings, out of 33 patients with MDRO acquisition at the time of hospital admission, only 1 patient informed the medical staff of their MDRO acquisition status. The introduction of a computerized system for sharing the medical information regarding MDRO acquisition among medical institutions would be useful. In the Republic of Korea, a universal health insurance covers all Korean citizens under a public health care insurance system of the National Health Insurance Corporation. Since 2015, patients' information on travel to areas at high risk of imported infectious diseases has been provided to medical institutions using the National Drug Utilization Review Program. Furthermore, infectious diseases caused by 6 types of MDROs have been legally designated for sentinel surveillance since 2010.[39] It is possible to consider the construction of a computerized system that uses these health policies that are already in place.

There are several limitations to our study. First, our study was performed at a single hospital in the Republic of Korea and enrolled a limited number of patients. Therefore, the results of this study cannot be generalized to other tertiary care settings owing to the heterogeneity in the prevalence of antimicrobial resistance. In this study, the 95% CI of the OR for percutaneous drainage was relatively large. This is because only 6 patients underwent percutaneous drainage. Therefore, this result should be interpreted with caution. Although LOOCV was performed to assess the predictive accuracy of the final model and the results seemed to be acceptable, studies involving larger numbers of study subjects are needed in the future. Second, only 192 patients (33.4%) of the 575 candidates for active surveillance were included in the study. The possibility of differences in the characteristics between the included and excluded patients cannot be completely ignored. Third, our results might overestimate the prevalence rates of MDROs, as our study population consisted of patients who had been hospitalized at health care facilities. Meanwhile, this study has a peculiar point of analyzing the risk factors for MDRO acquisition only in patients with hospital admissions within the last 90 days. Fourth, culturing a single body site can possibly lead to an underestimation of CRAB prevalence. The sensitivity of surveillance cultures culturing a single body site is low, even when multiple body sites are sampled.[40] In our study, nasopharyngeal swabs at a single body site were used for CRAB screening, as *Acinetobacter* species are known to be common commensals in the human pharynx and pneumonia is the most common clinical syndrome of CRAB infections.[40] Finally, there might be additional risk factors for MDRO acquisition that were not collected in our study and thus were not examined.

CONCLUSIONS

This study demonstrates a frequent occurrence of MDRO influx into an acute care hospital by patients who had been hospitalized at health care facilities. In addition, hospitalization for ≥60 days before admission, prior exposure to antibiotics within 90 days, cognitive dysfunction, percutaneous drainage, and underlying pulmonary diseases were significantly associated with isolation of MDROs at the time of hospital admission. Targeted screening for MDROs and preemptive isolation should be considered in this high-risk subgroup of newly admitted patients. However, depending on the epidemiology of individual MDROs and the condition of infection control resources, careful decisions should be made as to which MDRO the screening should be applied to. Further multicenter prospective studies with a higher number of study subjects are needed to develop better predictive models to identify patients colonized with MDROs at the time of hospital admission.

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