

Influencing Factors of Successful Eradication of Multidrug-Resistant *Acinetobacter baumannii* in the Respiratory Tract with Aerosolized Colistin

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Background: The increased prevalence of multidrug-resistant *Acinetobacter baumannii* (MDRAB) poses a worldwide treatment challenge. Although aerosolized colistin therapy for MDRAB pneumonia has attracted increasing interest, factors influencing successful eradication remain unclear.

Methods: This retrospective study evaluated 135 consecutively admitted adult patients showing positive respiratory secretion cultures for MDRAB who underwent aerosolized colistin therapy between January 2007 and November 2011. Possible factors related to pneumonia and MDRAB eradication were collected for analysis.

Results: Patients with successful MDRAB eradication on Day 14 had a shorter interval between the day the positive MDRAB sputum cultures were yielded and the day colistin inhalation treatment began (4.0 ± 2.5 vs. 7.3 ± 6.5 ; $p = 0.002$). Patients with a worsening chest X-ray on Day 7 of the colistin inhalation had a lower chance of 14-day MDRAB eradication [1/44 (2.3%) vs. 8/37 (21.6%); $p = 0.006$]. Patients with diabetes mellitus also had a lower chance of early MDRAB eradication [13/44 (29.5%) vs. 20/37 (54.1%); $p = 0.025$].

Conclusions: Early intervention using aerosolized colistin in patients with MDRAB pneumonia or colonization can achieve better eradication. (*Biomed J* 2014;37:269-283)

Key words: *acinetobacter baumannii*, aerosolized colistin, multidrug resistant

The increased prevalence of multidrug-resistant *Acinetobacter baumannii* (MDRAB) poses a worldwide challenge for treatment and infection control.^[1-3] MDRAB can colonize in the respiratory tracts or lead to nosocomial pneumonia.^[4]

MDRAB pneumonia has high mortality rates, and leads to increased hospital stay lengths and costs.^[5,6]

Colistin, a polypeptide antibiotic available since the 1960s, has rarely been used because of a high incidence of

At a Glance Commentary

Scientific background of the subject

Multidrug-resistant *Acinetobacter baumannii* (MDRAB) poses a worldwide challenge for treatment and infection control. Factors predicting successful eradication using aerosolized colistin remain unclear.

What this study adds to the field

Early intervention using aerosolized colistin in patients with MDRAB pneumonia or colonization can achieve better eradication. However, patients with diabetes mellitus had lower 14-day eradication rate and patients with worsening CXR on Day 7 of the colistin inhalation had a lower chance of early MDRAB eradication.

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nephrotoxicity reported in previous clinical data.^[7,8] Its usage has been restricted to the treatment and prevention of recurrent *Pseudomonas aeruginosa* pneumonia in patients with cystic fibrosis.^[9,10] However, increasing rates of resistance among Gram-negative bacteria to current empiric antibiotics and a subsequent high clinical failure rate has caused colistin to be re-evaluated for MDRAB infection treatment.^[11-14] Although intravenous (IV) colistin administration against MDRAB may yield high clinical and microbial success rates,^[15] recent studies have reported a nephrotoxicity rate of 10-30%.^[16,17] Use of aerosolized colistin to treat MDRAB pneumonia or to eradicate the pathogen from the respiratory tract has been tested.^[11-13,18] However, factors influencing successful eradication remain unclear.

In this study, we attempted to determine the factors influencing successful MDRAB eradication using aerosolized colistin.

METHODS

Patient population

This retrospective study was conducted at a 2500-bedded tertiary teaching hospital in southern Taiwan. According to our hospital guidelines, patients with a positive sputum culture for MDRAB are required to undergo contact isolation until two sets of successive sputum cultures yield negative results for MDRAB growth. We assessed all adult patients (age ≥ 18 years) who were admitted in the respiratory care center from January 2007 to November 2011 with at least one set of cultures from respiratory secretions (including sputum, trachea suction, and bronchial washing) that yielded MDRAB microbial growth. Patients were enrolled if they had received aerosolized (inhaled) colistin for more than 3 days after the day sputum culture yielded positive MDRAB growth. Control group of patients received other antibiotic therapies that did not include inhaled colistin or were given no antibiotic at all. Patients were excluded if they had concomitant MDRAB bacteremia because it required an IV antibiotic (instead of only aerosolized therapy), and no such patient received aerosolized (inhaled) colistin during our study period. Patients who died or were discharged within 14 days after the discovery of a positive MDRAB culture were excluded. To limit the confounding factors, patients who received IV colistin with or without aerosolized colistin were also excluded. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (permit number of IRB: 100-4062B), and the patient consent requirement was waived.

Colistin regimen

The aerosolized colistin dosage was 2 million international units (IU) (or 160 mg colistin methanesulfonate)^[11]

administered twice per day. No dose adjustment was made based on the patients' renal function. In spontaneously breathing patients, 2 million IU colistin was diluted in 4 ml normal saline and nebulized with 8 l/min oxygen flow. For patients with ventilator support, the aerosolized colistin was diluted in 2 ml of sterile normal saline (0.9%) and delivered via a ventilator.

Data collection and definition

Clinical data, including baseline patient characteristics, possible predisposing factors for MDRAB infection, bacteriological and clinical responses of MDRAB infection/colonization, and patient outcomes were retrospectively collected using a review of medical records. We compared the changes of the chest X-ray (CXR) and systemic inflammatory response syndrome (SIRS) scores between the first day of colistin inhalation treatment and 7 (± 2) days later. The interval between the day that the sputum culture yielded MDRAB and the day that the aerosolized colistin therapy began was also recorded.

Definition of multidrug resistance

Multidrug resistance was defined as isolates that were unsusceptible to all of the following antibiotics: Anti-pseudomonal penicillins, anti-pseudomonal cephalosporins, carbapenems, monobactams, quinolones, aminoglycosides, tetracycline, and trimethoprim/sulfamethoxazole.^[14,19]

Antimicrobial susceptibility of *A. baumannii* isolates was determined using the disk-diffusion test, as recommended by the National Committee for Clinical Standards.

Definition of colonization/pneumonia

Pneumonia was diagnosed based on the US Centers for Disease Control and Prevention criteria, with at least two or more of the following to be satisfied: (1) fever (body temperature $> 38.3^{\circ}\text{C}$); (2) leukocytosis (25% increase and $> 10000/\text{mm}^3$) or leukopenia (25% decrease and $< 5000/\text{mm}^3$); and (3) purulent tracheal secretion. One of the following criteria must also be satisfied: (1) new and persistent infiltrates appearing on the chest radiograph, (2) the same microorganisms are isolated from pleural fluid and tracheal secretions, (3) a radiographic cavitation, (4) histological proof of pneumonia, or (5) positive cultures from the bronchoalveolar lavage ($\geq 1 \times 10^4$ colony-forming units/ml).^[14,18]

The CXR and its change was defined as infiltration, consolidation, cavitations; improvement, stationary, or progression by one radiologist and one pulmonologist. If they had contradicting opinions, another senior pulmonologist was consulted. If the patients' clinical presentations did not meet the criteria for pneumonia, they were classified as colonization.

Definition of 14- or 28-day eradication

Sputum cultures were performed every 3-5 days from the day the sputum yielded positive growth for MDRAB. The 14-day eradication was defined as a minimum of two consecutive cultures from the respiratory secretions that revealed no MDRAB growth within 14 days.^[11] The 28-day eradication was defined as at least two consecutive cultures from the respiratory secretions that yielded no MDRAB growth within 28 days.^[11]

Definition of SIRS score

The SIRS score is a four-point score defined in this study, marking one point for each of the four components: (1) body temperature less than 36°C or greater than 38°C, (2) heart rate greater than 90 beats/min, (3) tachypnea (high respiratory rate) with a breathing rate greater than 20 breaths/min or an arterial partial pressure of carbon dioxide less than 32 mm Hg, (4) white blood cell count less than 4000 cells/mm³ (4×10^9 cells/l) or greater than 12,000 cells/mm³ (12×10^9 cells/l), or the presence of greater than 10% of immature neutrophils (band forms).^[20]

Statistical analysis

Categorical variables were analyzed using the Chi-square test or Fisher's exact test where appropriate, and continuous variables were compared using Student's *t*-test or the Mann-Whitney U test. Multivariate logistic regression analysis was performed to identify the factors for early MDRAB eradication. All variables that were considered risk factors with $p < 0.10$ in the univariate analysis were entered into the multivariate model. If individual variables associated with early MDRAB eradication had $p < 0.05$ in the multivariate model, a backward elimination procedure was used to identify the final independent factors. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were reported for logistic regression analysis. A two-tailed $p < 0.05$ was considered significant. All statistical analyses were performed using the SPSS 18.0 software package (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 240 patients with MDRAB growth from respiratory secretions were admitted to Kaohsiung Chang Gung Memorial Hospital from January 2007 to November 2011. Seventy-seven patients were excluded because concomitant MDRAB bacteremia was identified and those patients did not receive aerosolized colistin therapy. Another 28 patients were excluded because of concomitant use of IV colistin. The baseline characteristics for all 135 patients enrolled are shown in Table 1. There was no statistical difference between the aerosolized colistin group ($n = 81$)

and the control group ($n = 54$) regarding sex, age, severity score [Acute Physiological and Chronic Health Evaluation II (APACHE II)], and underlying comorbidities.

Fifty-two patients were diagnosed with MDRAB pneumonia, and 83 patients were diagnosed with MDRAB colonization. In addition, 27 patients in the aerosolized group received a concomitant IV antibiotic therapy (22 with Tigecycline and five with Unasyn).

The most commonly prescribed antibiotic for the control group patients was Tigecycline ($n = 40$), followed by Unasyn ($n = 12$). Two other patients did not receive antibiotic treatment, despite showing respiratory tract colonization with MDRAB.

Physicians preferred using aerosolized colistin compared to other IV antibiotics to eradicate MDRAB colonization (70.4% vs. 48.1%; $p = 0.009$). Physicians preferred using IV antibiotic, rather than aerosolized colistin, to treat MDRAB-induced pneumonia (51.9% vs. 29.6%; $p = 0.009$).

Outcomes between aerosolized group and control group

The early MDRAB eradication rate within 14 days after the first observation of MDRAB isolation from the respiratory secretions was higher in patients treated with aerosolized colistin than in patients treated with other medication [54.3% (44/81) vs. 29.6% (16/54); $p = 0.005$] [Table 2].

No difference was seen between the aerosolized colistin group and the control group patients for the respiratory tract MDRAB eradication rate on Day 28 [66.7% (54/81)

Table 1: Baseline patient characteristics

Variable	Aerosolized colistin $n=81$ (%)	Control $n=54$ (%)	<i>p</i> value
Age, mean years \pm SD	74.9 \pm 12.0	71.2 \pm 15.7	0.190
Male	50 (61.7)	27 (50.0)	0.177
Apache II score*, mean \pm SD	19.8 \pm 5.5	22.5 \pm 5.4	0.171
Colonization	57 (70.4)	26 (48.1)	0.009
Pneumonia	24 (29.6)	28 (51.9)	0.009
Smoking	14 (17.3)	8 (14.8)	0.704
Alcoholism	6 (7.4)	4 (7.4)	1.000
Diabetes mellitus	33 (40.7)	15 (27.8)	0.123
Hypertension	49 (60.5)	27 (50.0)	0.229
Coronary artery disease	19 (23.5)	9 (16.7)	0.340
Chronic kidney disease	16 (19.8)	13 (24.1)	0.549
Liver cirrhosis	3 (3.8)	2 (3.7)	0.989
COPD	18 (22.2)	6 (11.1)	0.098
Neoplastic disease	15 (18.5)	10 (18.5)	0.714
Stroke	24 (29.6)	11 (20.4)	0.229
Tuberculosis history	7 (8.6)	4 (7.4)	0.797
Tracheostomy	6 (7.4)	6 (11.1)	0.689

Abbreviations: SD: Standard deviation; APACHE: Acute physiology and chronic health evaluation; COPD: Chronic obstructive pulmonary disease; *: Apache II score was measured at days admitted to intensive care unit or respiratory care center

vs. 51.9% (28/54); $p = 0.084$]. In addition, there was no statistical difference in the 28-day mortality rate between patients treated with aerosolized colistin and the control group [11.3% (6/81) vs. 16.7% (8/54); $p = 0.167$].

In addition, no statistical difference in hospital mortality between patient groups was apparent [32.1% (26/81) vs. 40.7% (22/54); $p = 0.304$].

Predictors for early MDRAB eradication with aerosolized colistin

Sex, age, severity score (APACHE II), and tracheostomy status did not alter the eradication rate on Day 14 [Table 3]. However, analyzing the influence of underlying comorbidities on the 14-day MDRAB eradication showed that patients with diabetes mellitus (DM) had lower 14-day eradication rate [13/44 (29.5%) vs. 20/37 (54.1%); $p = 0.025$].

Patients with successful MDRAB eradication on Day 14 had a shorter interval between the day the sputum cultures yielded MDRAB positive growth and the day colistin inhalation treatment began (4.0 ± 2.5 vs. 7.3 ± 6.5 ;

Table 2: Outcomes of patients in aerosolized colistin group and control group

Variable	Aerosolized colistin <i>n</i> =81 (%)	Control <i>n</i> =54 (%)	<i>p</i> value
14-day eradication	44 (54.3)	16 (29.6)	0.005
28-day eradication	54 (66.7)	28 (51.9)	0.084
28-day mortality	6 (7.4)	8 (14.8)	0.167
In-hospital mortality	26 (32.1)	22 (40.7)	0.304
Duration of hospital stay, mean±SD	67.4±44.0	62.3±52.6	0.541

Abbreviation: SD: Standard deviation

Table 3: The influence of baseline characteristics on MDRAB eradication on day 14

Variable	14-day eradication <i>n</i> =44 (%)	Failed 14-day eradication <i>n</i> =37 (%)	Univariate analysis <i>p</i> value	Odds ratio (95% CI)	Multivariate analysis <i>p</i> value
Age, mean years±SD*	74.7±12.9	74.0±10.9	0.808		
Male	28 (63.6)	22 (59.5)	0.700	1.2 (0.5-2.9)	
Apache II score†, mean±SD*	24.0±5.9	23.5±5.0	0.697		
Smoking	10 (22.7)	4 (10.8)	0.158	2.4 (0.7-8.5)	
Alcoholism	3 (6.8)	3 (8.1)	0.825	0.8 (0.2-4.4)	
Diabetes mellitus	13 (29.5)	20 (54.1)	0.025	0.4 (0.1-0.9)	0.041
Hypertension	27 (61.4)	22 (59.5)	0.861	1.1 (0.4-2.6)	
Coronary artery disease	11 (25.0)	8 (21.6)	0.721	1.2 (0.4-3.4)	
Chronic kidney disease	6 (13.6)	10 (27.0)	0.132	0.4 (0.1-1.3)	
Liver cirrhosis	0 (0)	3 (8.3)	0.087	0 (0-0)	0.999
COPD‡	11 (25.0)	7 (18.9)	0.512	1.4 (0.5-4.1)	
Neoplastic disease	10 (22.7)	5 (13.5)	0.351	1.9 (0.6-6.1)	
Stroke	11 (25.0)	13 (35.1)	0.320	0.6 (0.2-1.6)	
Tuberculosis history	6 (13.6)	1 (2.7)	0.797	5.7 (0.7-50)	
Tracheostomy	3 (6.8)	3 (8.1)	0.689	0.8 (0.2-4.4)	

Abbreviations: MDRAB: Multidrug-resistant *Acinetobacter baumannii*; SD: Standard deviation; APACHE, Acute physiology and chronic health evaluation; COPD: Chronic obstructive pulmonary disease; *: Apache II score was measured at days admitted to intensive care unit or respiratory care center

$p = 0.002$) [Figure 1]. In addition, the status of the pneumonia or respiratory tract colonization with MDRAB did not affect the 14-day eradication rate. However, the CXR resolution on Day 7 cannot be used to determine whether the MDRAB in the respiratory tract can be eradicated on Day 14, and patients with a worsening CXR on Day 7 of the colistin inhalation had a lower chance of early MDRAB eradication [1/44 (2.3%) vs. 8/37 (21.6%); $p = 0.006$] [Table 4]. The same result was also found with regard to SIRS score; improved score on Day 7 cannot be used to determine whether the MDRAB in the respiratory tract can be eradicated on Day 14, and patients with a worsening SIRS score on Day 7 of the colistin inhalation had a borderline

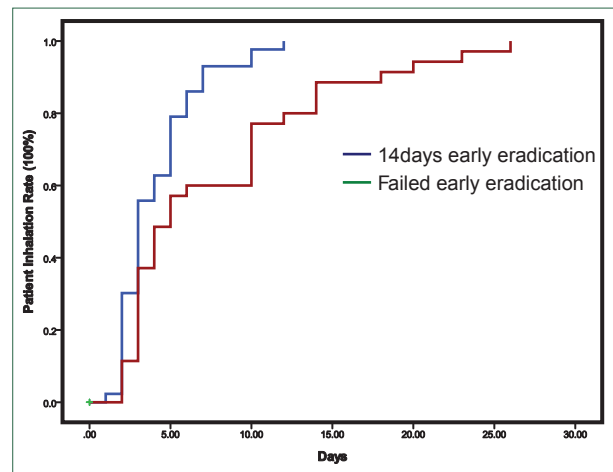


Figure 1: Cumulative percentage of patients started on inhalation colistin after the sputum culture yielded multidrug-resistant *Acinetobacter baumannii* between successful and failed 14-day eradication groups.

Table 4: The clinical status and their influences on 14-day MDRAB eradication with aerosolized colistin

Variable	14-day eradication n=44 (%)	Failed 14-day eradication n=37 (%)	Univariate analysis p value	OR (95% CI)	Multivariate analysis p value	OR
CXR improving	22 (50.0)	15 (40.5)	0.395	1.5 (0.6-3.5)		
CXR stationary	21 (47.7)	14 (37.8)	0.371	1.5 (0.6-3.7)		
CXR worsening	1 (2.3)	8 (21.6)	0.006	11.9 (1.4-100) [§]	0.029	12.0
SIRS score improving	11 (25.0)	9 (24.3)	0.944	1.0 (0.4-2.9)		
SIRS score stationary	27 (61.4)	17 (45.9)	0.165	1.9 (0.8-4.5)		
SIRS score worsening	6 (13.6)	11 (29.7)	0.076	2.7 (0.9-8.1) [§]	0.108	2.8
Culture-inh days*	4.0±2.5	7.3±6.5	0.002		0.005	
Colonization	32 (72.7)	25 (67.6)	0.612	1.3 (0.5-3.3)		
Pneumonia	12 (27.3)	12 (36.4)	0.612	0.8 (0.3-2)		

Abbreviations: MDRAB: Multidrug-resistant *Acinetobacter baumannii*; SIRS: Systemic inflammatory response syndrome; *: Culture-inh days: The interval between the first day that the positive sputum culture for MDRAB was yielded and the first day of the colistin inhalation treatment;

‡: OR rate was presented as: failed eradication/success eradication

lower chance of early MDRAB eradication [4/44 (13.6%) vs. 11/37 (29.7%); $p = 0.076$]. On multivariate analysis, shorter interval between the day that the sputum culture yielded MDRAB positive growth and the day that the aerosolized colistin therapy began ($p = 0.005$), and worsening CXR on Day 7 of the colistin inhalation ($p = 0.029$) still showed a significant lower chance of early MDRAB eradication, but worsening SIRS score on Day 7 was no more a influencing factor of failed MDRAB eradication ($p = 0.108$).

DISCUSSION

54.3% of the patients receiving inhalation colistin for MDRAB had achieved the goal of 14-day eradication. High MDRAB respiratory tract eradication rate using inhalation colistin observed in this study was consistent with previous cohort studies.^[11-13]

In colistin inhalation group, 27 of 81 patients had concomitant use of IV antibiotics. After 27 patients who with concomitant IV antibiotics were excluded, colistin inhalation group still had higher 14-day eradication than the control group [61.1% (33/54) vs. 29.6% (16/38); $p = 0.001$]. Since eradication rate was higher in patients with inhalation alone than in those with combined inhalation with IV antibiotics [61.1% (33/54) vs. 40.7% (11/27)], synergistic or additive effect did not seem to exist.

Although aerosolized colistin has been used to eradicate MDRAB from the respiratory tract,^[11,13,14,18] we further determined the influencing factors for successful eradication. This retrospective analysis yielded three main findings. First, early intervention using aerosolized colistin in patients with MDRAB-induced pneumonia or colonization can achieve better eradication. Second, patients with DM receiving aerosolized colistin for MDRAB-induced colonization or pneumonia showed worse eradication results. Third, the progression of CXR on Day 7 may predict failed early eradication.

Early prediction of the eradication outcomes of patients with MDRAB colonization or pneumonia enables prompt adjustment of the treatment strategy and a more efficient allocation of medical resources. In addition, early prediction can help control infection and reduce the outbreak of MDRAB. Our study results may be applied to clinical practice because we attempted to use colistin inhalation when the sputum culture grew MDRAB at first and decided whether to continue colistin inhalation on Day 7 after reviewing the CXR change. If the CXR progressed, the inhalation colistin treatment was changed to IV colistin, Tigecycline, or a combined inhaled and IV colistin to enhance MDRAB eradication.^[7,15,21-24]

We found that patients with early eradication showed a shorter interval between the day that the sputum culture yielded positive MDRAB growth and the day that the aerosolized colistin therapy began. This may be explained as the longer the interval between positive cultures and the beginning of inhalation, the more the bacterial load. In addition, biofilm formation caused by delaying colistin inhalation may make MDRAB eradication more difficult.^[25-27]

We also investigated how long the colistin inhalation should be used if early eradication was not achieved. In our study, 44 (54.3%) of 81 patients treated with aerosolized colistin had early eradication. However, if early eradication was not achieved, prolonged use of aerosolized colistin benefited an extra 27.0% (10/37) of patients with 28-day MDRAB eradication. For acute kidney injury, no statistically significant difference was found between patients treated with aerosolized colistin and those treated with other medications [38.1% (24/63) vs. 30.6% (11/36); $p = 0.576$], which is comparable with other study results.^[11-13] During the study period, no bronchospasm was found in patients with colistin inhalation, consistent with the results of previous clinical studies.^[11-13] Thus, we suggest that for patients who cannot achieve early eradication with a stable clinical status,

receiving prolonged treatment using aerosolized colistin (for up to 28 days) is reasonable.

We also found patients with DM had lower 14-day eradication rate. Patients with DM are considered to be immunocompromised due to disturbances in cellular innate immunity.^[28,29] Furthermore, some microorganisms (e.g., *Candida albicans*) become more virulent in a high glucose environment.^[28,29]

A number of limitations should be mentioned when interpreting the results of this study. First, the retrospective design of the study may have omitted factors influencing the eradication outcome, and we did not interfere in the antibiotic treatments used for MDRAB. Second, patients who were included in our analysis consisted of a heterogeneous population with a variety of sources and hospitalization duration before acquiring MDRAB. On the other hand, it can reflect the reality that patients with MDRAB colonization or pneumonia come from heterogeneous populations. Third, patients treated with IV colistin were excluded to avoid the IV treatment influence on MDRAB eradication. In the aerosolized colistin group, 33% of the patients had concomitant usage of IV antibiotics (22 patients used Tigecycline and 5 patients used Unasyn); in the control group, 74% patients received IV antibiotics (40 patients received Tigecycline). When considering the influence of the concomitant IV antibiotics, the eradication rate may have been lower in the control group than in the aerosolized colistin group because more patients used IV antibiotics in the control group. However, a recent study showed a comparable eradication rate between a treatment that combined concomitant aerosolized and IV colistin and the one that consisted solely of IV colistin in patients with ventilator-associated pneumonia.^[24] Fourth, there was a high percentage of patients with colonization in colistin inhalation group than in IV antibiotics group [70.4% (57/81) vs. 48.1% (26/54); $p = 0.009$]. We cannot deny that the higher 14-day eradication rate of MDRAB for colistin inhalation group is due to the difference in severity in both groups since higher colonization percentage accounts for the higher eradication rate. A matched case-control study showed higher 14-day MDRAB eradication rate in colistin inhalation group and control group [84.6% (33/39) vs. 10.3% (4/39); $p < 0.001$] regardless of the percentage of colonization.^[11]

In conclusion, early intervention for patients with MDRAB pneumonia or colonization using aerosolized colistin may achieve a higher eradication rate. If the CXR progressed on Day 7 of colistin inhalation therapy, early eradication failure may occur.

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