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Mupirocin-Resistant, Methicillin-Resistant *Staphylococcus aureus* Strains in Canadian Hospitals[▽]

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Mupirocin resistance in *Staphylococcus aureus* is increasingly being reported in many parts of the world. This study describes the epidemiology and laboratory characterization of mupirocin-resistant methicillin-resistant *S. aureus* (MRSA) strains in Canadian hospitals. Broth microdilution susceptibility testing of 4,980 MRSA isolates obtained between 1995 and 2004 from 32 Canadian hospitals was done in accordance with CLSI guidelines. The clinical and epidemiologic characteristics of strains with high-level mupirocin resistance (HLMup^r) were compared with those of mupirocin-susceptible (Mup^s) strains. MRSA strains were characterized by pulsed-field gel electrophoresis (PFGE) and typing of the staphylococcal chromosomal cassette *mec*. PCR was done to detect the presence of the *mupA* gene. For strains with *mupA*, plasmid DNA was extracted and subjected to Southern blot hybridization. A total of 198 (4.0%) HLMup^r MRSA isolates were identified. The proportion of MRSA strains with HLMup^r increased from 1.6% in the first 5 years of surveillance (1995 to 1999) to 7.0% from 2000 to 2004 ($P < 0.001$). Patients with HLMup^r MRSA strains were more likely to have been aboriginal (odds ratio [OR], 3.7; 95% confidence interval [CI], 1.5 to 9.4; $P = 0.006$), to have had community-associated MRSA (OR, 2.2; 95% CI, 1.0 to 5.0; $P = 0.05$), and to have been colonized with MRSA (OR, 1.7; 95% CI, 1.0 to 3.0; $P = 0.04$). HLMup^r MRSA strains were also more likely to be resistant to fusidic acid (21% versus 4% for mupirocin-susceptible strains; $P < 0.001$). All HLMup^r MRSA strains had a plasmid-associated *mupA* gene, most often associated with a 9-kb HindIII fragment. PFGE typing and analysis of the plasmid profiles indicate that both plasmid transmission and the clonal spread of HLMup^r MRSA have occurred in Canadian hospitals. These results indicate that the incidence of HLMup^r is increasing among Canadian strains of MRSA and that HLMup^r MRSA is recovered from patients with distinct clinical and epidemiologic characteristics compared to the characteristics of patents with Mup^s MRSA strains.

Mupirocin is a topical antimicrobial agent that interferes with protein synthesis by competitive inhibition of bacterial isoleucyl-tRNA synthetase (42). It has been used to treat skin and soft tissue infections and to eradicate staphylococcal carriage in health care workers and patients (7). Intranasal mupirocin has also been used preoperatively to prevent surgical site infections (17, 19, 28, 41) and to control the transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) in health care facilities (2, 14, 18, 40). However, the prevalence of mupirocin resistance in MRSA has increased in settings with extensive use of this agent (8, 22, 38), and it has also been reported in community-associated MRSA strains (13). In Canada, high-level mupirocin resistance has recently been reported in more than 50% of community-associated strains identified in an outbreak in northern Saskatchewan (23).

Although no performance standards or interpretive criteria have been published for mupirocin susceptibility testing, mupirocin resistance in staphylococci is commonly defined as low-level resistance (MICs, 8 to 256 μg/ml) or high-level resistance (MICs, ≥512 μg/ml) (3, 16). Low-level resistance is usually associated with point mutations in the chromosomally encoded *ileS* gene (10, 36), whereas high-level resistance is generally due to a plasmid-mediated gene, *mupA* (also referred to as *ileS2*), which encodes an additional modified isoleucyl-tRNA synthetase (15, 36). Treatment with mupirocin is not likely to be effective in the presence of high-level mupirocin resistance (6, 34, 39), and there is some evidence to suggest that low-level resistance may also predict treatment failure (39). In one study involving patients undergoing long-term peritoneal dialysis, the development of mupirocin resistance was associated with an increased risk of staphylococcal infections (26).

In this report, we describe the epidemiology and clinical features of hospitalized patients with high-level mupirocin-resistant MRSA strains in a network of Canadian hospitals between 1995 and 2004. We also characterized these strains in order to determine the molecular epidemiology and mechanisms of mupirocin resistance.

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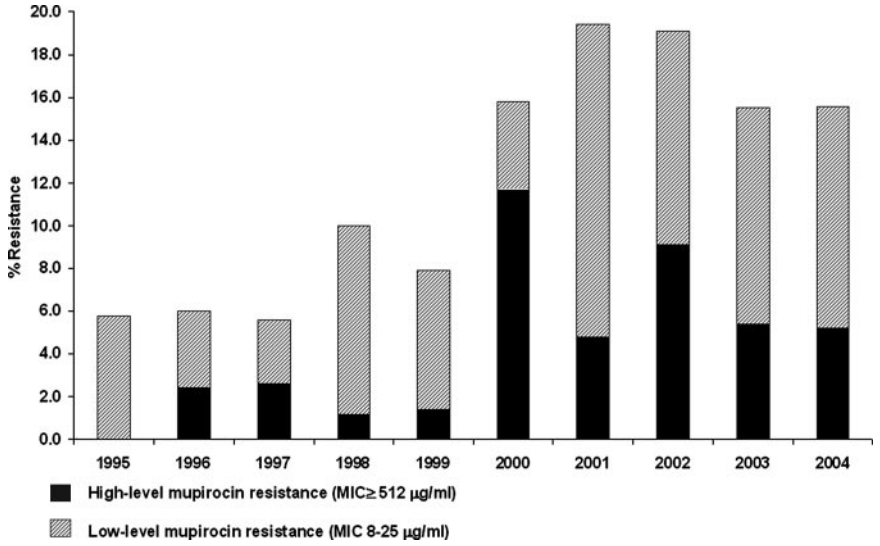

FIG. 1. Annual rates of mupirocin resistance in MRSA strains recovered from Canadian hospitals, 1995 to 2004.

MATERIALS AND METHODS

Surveillance for MRSA has been conducted by hospitals in Canada participating in the Canadian Nosocomial Infection Surveillance Program since January 1995. The surveillance methods used have been described previously (32, 33). When a new case of MRSA infection or colonization in an inpatient was identified, the infection control practitioner used a standardized data collection form to abstract demographic and clinical information from the medical records. The presence of infection caused by MRSA was determined by the infection control practitioner using standard definitions (11). The site of MRSA acquisition (health care facility or community) was determined by using previously published criteria (9). The designation of isolates as community acquired was based on epidemiologic data and the absence of established risk factors for health care-associated MRSA, prior to knowledge of the molecular strain typing results. Demographic, clinical, and epidemiologic data for patients with high-level mupirocin-resistant MRSA were compared with those for patients with mupirocin-susceptible MRSA (excluding those with low-level mupirocin resistance).

The first MRSA isolate from each patient was sent to a central laboratory for additional testing. The isolates were confirmed to be MRSA by detection of the *mecA* and *nuc* genes by a multiplex PCR assay (21). Antimicrobial susceptibility testing was done by broth microdilution methods in accordance with Clinical and Laboratory Standards Institute guidelines (5). Inducible resistance to clindamycin in macrolide-resistant strains of MRSA was detected by a standardized disk approximation test (5). MRSA strains were typed by pulsed-field gel electrophoresis (PFGE) with SmaI digests of genomic DNA; DNA profiles were digitized and analyzed with BioNumerics software, version 3.5 (Applied Maths, Austin, TX) (33). Typing of the staphylococcal chromosomal cassette *mec* (SCC*mec*) was done by PCR with primers and by the methods published previously (24).

The *mupA* gene was detected in DNA extracts by PCR with primers and by the methods described previously (1). Plasmid DNA was extracted by using a High Pure plasmid isolation kit (Roche Diagnostics, Laval, Quebec, Canada), but with a modification to the manufacturer's instructions, in which lysostaphin was added in the lysis step of the procedure. Purified plasmid DNA was eluted in 50 μl of TE (Tris-EDTA) buffer. The plasmids were restricted with HindIII for 1 h, separated on a 1% agarose gel in 0.5× TAE (Tris-acetate-EDTA) at 60 V for 3 h, and transferred onto a Hybond N^+ membrane (GE Healthcare, Piscataway, NJ). The membrane was probed with a 458-bp PCR-amplified *mupA* gene probe by using an enhanced chemiluminescence direct nucleic acid labeling and detection system (GE Healthcare). HindIII restriction fragment length polymorphisms were examined and assigned profile descriptors.

Statistical analyses were done by Student's *t* test, the chi-square test, and Fisher's exact test, as appropriate. All statistical tests were two tailed, with a *P* value of ≤ 0.05 considered statistically significant. A multivariate logistic regression analysis was done and included variables with *P* values of <0.20 in the univariate analysis. All analyses were done with SPSS software, version 11.0.

RESULTS

A total of 4,980 unique patient MRSA isolates recovered from 32 Canadian Nosocomial Infection Surveillance Program hospitals between 1995 and 2004 were available for antimicrobial susceptibility testing. Of these, 198 (4.0%) were found to have high-level resistance to mupirocin, 396 (8.0%) had low-level mupirocin resistance, and 4,386 were susceptible to mupirocin. The proportion of isolates that were resistant to mupirocin increased over time (Fig. 1). In the first 5 years of surveillance (1995 to 1999), 46 (1.6%) MRSA strains had high-level resistance, whereas the rates increased nearly fivefold to 7.0% among isolates recovered from 2000 to 2004 ($P < 0.001$). The rates of low-level mupirocin resistance also increased during this time, from 6.4% (1995 to 1999) to 10.0% (2000 to 2004) ($P < 0.001$). MRSA strains with high-level resistance were identified in 17 hospitals across the country (representing 53% of the hospitals with MRSA in the surveillance), with rates ranging from 0 to 26% (median, 3%) among the MRSA strains tested. Isolates from five hospitals from geographically diverse regions of the country accounted for 72% of all the MRSA isolates with high-level resistance to mupirocin; only 38% of all the MRSA isolates identified were reported from these five hospitals.

Complete clinical and epidemiologic data were available for 139 (70%) patients with high-level mupirocin resistant MRSA and for 3,187 (73%) patients with mupirocin-susceptible MRSA. The demographic and clinical characteristics of these patients are summarized in Table 1. In the multivariate analysis, the detection of high-level mupirocin-resistant MRSA strains was found to be associated with being a native aboriginal (odds ratio [OR], 3.71; 95% confidence interval [CI], 1.51 to 9.36; $P = 0.006$), with having a community-associated isolate (OR, 2.24; 95% CI, 1.02 to 4.96; $P = 0.05$), and with having been colonized rather than infected with MRSA (OR, 1.74; 95% CI, 1.02 to 2.99; $P = 0.04$) (Table 2).

The antimicrobial susceptibility test results for mupirocin-

TABLE 1. Demographic and clinical characteristics of hospitalized patients with mupirocin-susceptible and mupirocin-resistant MRSA strains, 1995 to 2004[a]

Characteristic	Patients with mupirocin-susceptible MRSA	Patients with mupirocin-resistant MRSA	OR (95% CI)	*P* value
No. of patients	3,187	139		
Median age (yr)	69.6	71.6		0.40
No. (%) males	1,918 (60)	91 (66)	1.2 (0.9–1.8)	0.26
No. (%) of patients of aboriginal ethnicity	92 (3)	20 (18)	6.3 (3.7–10.7)	<0.001
No. (%) of patients with community-associated MRSA	134 (6)	13 (14)	2.5 (1.4–4.6)	0.003
No. (%) of patients from the following region of country:				
East[b]	162 (5)	2 (1)		
Central[c]	1,931 (61)	94 (68)		
West[d]	1,094 (34)	43 (31)		0.08
No. (%) of patients with MRSA infection	1,064 (33)	34 (24)	0.7 (0.5–1.1)	0.11
No. (%) of patients from whom MRSA was recovered from the following anatomic site:				
Blood	186 (6)	2 (1)	0.24 (0.06–0.96)	0.03
Sputum	648 (20)	18 (13)	0.58 (0.35–0.96)	0.03
Urine	281 (9)	12 (9)	0.98 (0.53–1.78)	0.94
Surgical site	391 (12)	14 (10)	0.80 (0.46–1.40)	0.44
Skin or soft tissue	921 (29)	39 (28)	0.96 (0.66–1.40)	0.92
Nose	1,333 (42)	60 (43)	1.06 (0.75–1.49)	0.75
Perineum or groin	433 (14)	24 (17)	1.33 (0.85–2.09)	0.27
Other site	772 (24)	25 (18)	0.69 (0.44–1.07)	0.09

[a] Mupirocin susceptible, MIC ≤ 4 μg/ml; mupirocin resistant, MIC ≥ 512 μg/ml.
[b] East, provinces of Nova Scotia, New Brunswick, and Newfoundland.
[c] Central, provinces of Quebec and Ontario.
[d] West, provinces of Manitoba, Saskatchewan, Alberta, and British Columbia.

susceptible and mupirocin-resistant MRSA isolates are summarized in Table 3. Resistance to vancomycin or linezolid was not identified. Compared to mupirocin-susceptible strains of MRSA, strains with high-level mupirocin resistance were more likely to be susceptible to tetracycline (7% versus 23%; $P < 0.001$), trimethoprim-sulfamethoxazole (10% versus 40%; $P < 0.001$), and ciprofloxacin (75% versus 90%; $P < 0.001$). Mupirocin-resistant strains were more likely to be resistant to fusidic acid (21% versus 4%; $P < 0.001$).

Most (73%) strains with high-level resistance to mupirocin possessed SCC*mec* type II; and the predominant DNA profile, as determined by PFGE, was CMRSA-2, accounting for 30.3% of the isolates (Table 4). This PFGE profile is identical to or closely related to U.S. PFGE type USA100/800, sequence type 5 (ST5) (4, 33), and was also the most common among the mupirocin-susceptible strains of MRSA. A strain designated CMRSA-9 (SCC*mec* type II; ST8) was also relatively common, accounting for 20.7% of the strains with high-level resistance, although most of these were recovered from patients at two hospitals located in the same city. Compared to the mupirocin-susceptible strains, mupirocin-resistant MRSA strains were more likely to be CMRSA-9 (20.7% versus 0.5%; $P < 0.001$) and less likely to be CMRSA-1 (USA600; ST45) (10.1% versus 31.2%; $P < 0.001$). Clustering of strains, as determined by PFGE, occurred commonly within hospitals (data not shown).

In total, only 7% of all isolates were thought to have been community acquired on the basis of epidemiologic criteria (9), and 14% of these isolates were found to have high-level mupirocin resistance. However, only 135 (2.7%) isolates had PFGE profiles of CMRSA-10 (USA300; ST8) or CMRSA-7 (USA400; ST1), the most commonly identified community-associated clones in North America. Only 1 of the 74 CMRSA-10 strains had high-level mupirocin resistance. However, 15 (25%) of the CMRSA-7 strains were mupirocin resistant, and mupirocin-resistant MRSA strains were more likely

TABLE 2. Multivariate analysis of variables associated with high-level mupirocin resistance in MRSA strains

Variable	OR (95% CI)	*P* value
Aboriginal ethnicity	3.71 (1.51–9.36)	0.006
Community-associated MRSA	2.24 (1.02–4.96)	0.05
MRSA colonization, without infection	1.74 (1.02–2.99)	0.04

TABLE 3. Antimicrobial susceptibilities of mupirocin-susceptible and mupirocin-resistant MRSA strains recovered from hospitalized patients, 1995 to 2004

Antimicrobial agent	Mupirocin-susceptible MRSA (n = 4,386)[a]		Mupirocin-resistant MRSA (n = 198)[b]		P value
	MIC_{90} (μg/ml)	% Resistant	MIC_{90} (μg/ml)	% Resistant	
Mupirocin	0.5	0	>512	100	
Erythromycin	>8.0	94	>8.0	86	
Clindamycin	>8.0	86	>8.0	85	
Linezolid	1.0	0	2.0	0	
Tetracycline	>16.0	23	<4.0	7	<0.001
Trimethoprim-sulfamethoxazole	>8.0	40	2.0	10	<0.001
Ciprofloxacin	>8.0	90	>8.0	75	<0.001
Rifampin	<0.5	2	<0.5	4	
Fusidic acid[c]	0.5	4	>8.0	21	<0.001
Vancomycin	1.0	0	1.0	0	

[a] Mupirocin susceptible, MIC ≤ 4.0 μg/ml.
[b] Mupirocin resistant, MIC ≥ 512 μg/ml.
[c] Fusidic acid provisional susceptibility breakpoint, MIC ≤ 0.5 μg/ml.

than mupirocin-susceptible strains to be CMRSA-7 (8% versus 1%; $P < 0.001$).

Of the 198 strains with high-level resistance to mupirocin, 144 (73%) were SCC*mec* type II, 44 (22%) were SCC*mec* type IV, six (3%) were SCC*mec* type III, and four were SCC*mec* type I. The predominant PFGE DNA profiles and corresponding SCC*mec* types are summarized in Table 5.

A total of 46 different plasmid profiles were identified in strains with high-level mupirocin resistance, as determined by HindIII restriction. Five plasmid types (designated plasmid profiles A, B, D, G, and H) accounted for 71% of all the isolates (Table 5; Fig. 2). These plasmid profiles had a wide distribution in hospitals across the country, although plasmid profile A was identified only in hospitals in Ontario and Quebec, whereas profile G, associated with CMRSA-7, was seen only in hospitals in western Canada.

The *mupA* gene was detected by PCR in total DNA extracted from the cells and from plasmid DNA in all of the 198 MRSA strains with high-level mupirocin resistance. The *mupA* gene probe most often hybridized with HindIII fragments of just under 9 kb in size (Fig. 2). However, all CMRSA-9 isolates had *mupA* HindIII-digested fragments approximately 12 kb in size, and most (11 of 15) CMRSA-7 (USA400) strains had fragments approximately 15 kb in size. The *mupA* gene was not detected in any of the 104 MRSA strains with low-level resistance that were assayed or in the 117 strains susceptible to mupirocin.

TABLE 4. Distribution of PFGE DNA profiles of MRSA isolates recovered in Canadian hospitals, 1995 to 2004

PFGE profile (U.S. PFGE type; MLST)[a]	% of strains	
	Mupirocin susceptible	High-level mupirocin resistant
CMRSA-1 (USA600; ST45)	31.2	10.1[b]
CMRSA-2 (USA100/800; ST5)	38.4	30.3
CMRSA-5 (USA500; ST8)	5.4	7.4
CMRSA-7 (USA400; ST1)	0.9	7.6[b]
CMRSA-9 (ST8)	0.5	20.7[b]
CMRSA-10 (USA300; ST8)	1.5	0.5
Others	22.1	23.4

[a] Data are from references 4 and 33. MLST, multilocus sequence type.
[b] $P < 0.001$.

DISCUSSION

In the past few years, mupirocin resistance has been increasing among staphylococci in many parts of the world (6, 8, 27, 37, 43). The risk of the emergence of such resistance appears to be greater among methicillin-resistant strains of *S. aureus* than among methicillin-susceptible strains (3, 31) and is often associated with the widespread use of mupirocin (8, 22, 38). In this study, an increase in both high-level and low-level mupirocin resistance was identified over 10 years in MRSA isolates recovered from patients in Canadian hospitals. The isolates with high-level mupirocin resistance were characterized by PFGE and determination of *mupA* gene-associated plasmid profiles. We found that MRSA isolates with high-level mupirocin resistance were nearly four times more likely to be recovered from those with an aboriginal ethnicity and from patients who were colonized with MRSA without evidence of

TABLE 5. PFGE DNA patterns, SCC*mec* types, and *mupA* restriction fragment length polymorphism (HindIII restriction profiles) of predominant Canadian MRSA strains with high-level mupirocin resistance

PFGE profile (U.S. PFGE type; MLST type; no. of isolates)[a]	SCC*mec* type (no. of isolates)	Plasmid profile (no. of isolates)
CMRSA-2 (USA100/800, ST5; 66)	II (53) IV (13) Other (18)	B (46) H (2)
CMRSA-9 (ST8; 54)	II (54) D (7) Other (3)	H (44)
CMRSA-1 (USA600, ST45; 20)	II (17) IV (3)	A (17) Other (3)
CMRSA-7 (USA400, ST1; 15)	IV (15) Other (3)	G (12)

[a] Data are from references 4 and 33. MLST, multilocus sequence type.

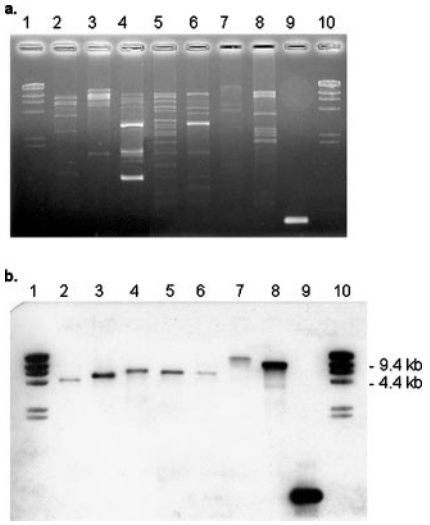

FIG. 2. (a) HindIII-restricted plasmid profiles of representative MRSA isolates with (b) corresponding *mupA* hybridization.

infection. Mupirocin resistance in MRSA was also more likely to be identified in strains thought to have been community acquired, based on epidemiologic criteria. It is important to note that this study included isolates obtained prior to 2005. The emergence and spread of community-associated clones (USA300 or USA400) in Canada has occurred only since 2004, and these strains are still not as prevalent in Canada as they are in many U.S. centers (4, 12, 23). Therefore, only a relatively small number of these community-associated strains were available for inclusion in this study. Although CMRSA-10 (USA300) strains were rarely mupirocin resistant, one-quarter of the CMRSA-7 (USA400) strains had high-level mupirocin resistance.

MRSA strains with mupirocin resistance were often found to be more susceptible to other antimicrobial agents, such as tetracycline and trimethoprim-sulfamethoxazole. This observation is also consistent with the association of mupirocin resistance in MRSA with community acquisition. In contrast, mupirocin-resistant isolates were more likely to be resistant to fusidic acid. It is tempting to speculate that the *fusB* determinant, which is responsible for fusidic acid resistance (25), is on the same plasmid as the *mupA* gene in isolates with high-level mupirocin resistance, but our study was not able to address this issue.

As in previous investigations done in the United States, we also found that high-level mupirocin resistance occurred in a variety of MRSA strains (as determined by PFGE) from different geographic regions of the country (30) and that transmission of the same strain was more likely to occur within a health care facility (3, 20, 29, 43). However, even within an institution, high-level mupirocin resistance often appeared to arise from multiple clones. We did not identify a chromosomal location of the *mupA* gene in any of our isolates, as has occasionally been described by Udo et al. (35). All Canadian strains of MRSA with high-level mupirocin resistance possessed a plasmid-associated *mupA* gene, but the plasmids were of various sizes and had various HindIII restriction digest profiles. Some plasmid profiles were associated with specific PFGE patterns and were more commonly found in certain geographic regions of the country. These findings suggest that both plasmid transmission and the clonal spread of mupirocin-resistant MRSA strains have occurred in Canadian hospitals, as has been reported previously in other countries (3, 20, 43). In this study, the *mupA* gene usually hybridized to a HindIII fragment of approximately 9 kb in size or less. In reports from Spain, Poland, South Korea, and the United States, the most common previously reported plasmid-derived HindIII fragments that contained *mupA* ranged in size from 4.5 kb to 10 kb (3, 20, 30, 43).

This surveillance for mupirocin resistance in MRSA included a large sample of both clinical and surveillance isolates recovered from patients in 32 hospitals across Canada over 10 years. However, the surveillance represented a convenience sample of hospital sites, and only the initial MRSA isolates recovered from hospitalized patients were included in the study. The results may not be representative of those for MRSA strains from outpatients or residents of long-term care facilities. A major limitation of the analysis of the variables associated with mupirocin resistance was the lack of information regarding the utilization of mupirocin or other antimicrobial agents. Complete clinical and epidemiologic data regarding the variables associated with mupirocin resistance were available for only 70% of the cases, although there is no reason to believe that the characteristics of patients with missing data were any different from those of the patients whose strains were included in the analysis. Although not all the MRSA isolates were available, a large number were characterized in this study and are likely to be representative of the MRSA strains from the participating hospitals in Canada.

In summary, the results of this study indicate that the rate of mupirocin resistance has been increasing among Canadian strains of MRSA. Continued surveillance for mupirocin resistance is important in order to retain the usefulness of this agent for the treatment and prevention of staphylococcal infections.

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