

High Prevalence of Mupirocin Resistance in *Staphylococcus aureus* Isolates from a Pediatric Population

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Topical mupirocin is used widely to treat skin and soft tissue infections and to eradicate nasal carriage of methicillin-resistant *Staphylococcus aureus* (MRSA). Few studies to date have characterized the rates of *S. aureus* mupirocin resistance in pediatric populations. We retrospectively studied 358 unique *S. aureus* isolates obtained from 249 children seen in a predominantly outpatient setting by the Division of Pediatric Dermatology at a major academic center in New York City between 1 May 2012 and 17 September 2013. Mupirocin resistance rates and the associated risk factors were determined using a logistic regression analysis. In our patient population, 19.3% of patients had mupirocin-resistant *S. aureus* isolates at the time of their first culture, and 22.1% of patients with *S. aureus* infection had a mupirocin-resistant isolate at some time during the study period. Overall, 31.3% of all *S. aureus* isolates collected during the study period were resistant to mupirocin. Prior mupirocin use was strongly correlated (odds ratio [OR] = 26.5; $P = <0.001$) with mupirocin resistance. Additional risk factors for mupirocin resistance included methicillin resistance, atopic dermatitis (AD), epidermolysis bullosa (EB), immunosuppression, and residence in northern Manhattan and the Bronx. Resistance to mupirocin is widespread in children with dermatologic complaints in the New York City area, and given the strong association with mupirocin exposure, it is likely that mupirocin use contributes to the increased resistance. Routine mupirocin testing may be important for MRSA decolonization strategies or the treatment of minor skin infections in children.

Mupirocin is a topical antibiotic widely used to treat skin and soft tissue infections and to eliminate nasal carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) (1). Mupirocin was introduced into clinical practice in 1985, with mupirocin-resistant *S. aureus* (MupRSA) first reported in 1987 (2, 3). Resistance is classified into two categories: low-level resistance, with MICs ranging from 8 to 256 $\mu\text{g/ml}$, and high-level resistance, with MICs of $\geq 512 \mu\text{g/ml}$. High-level resistance is in most cases conferred by the plasmid-borne gene *mupA*, which produces a “eukaryotic-like” tRNA synthetase with no affinity for mupirocin (4). A related gene, *mupB*, has also been shown to confer high-level resistance (5). Carriage of a high-level-resistant MupRSA strain has been shown to predict decolonization failure after treatment with mupirocin (6, 7). Low-level mupirocin resistance is due to point mutations in the native isoleucyl-tRNA synthetase gene (*ileS*), most commonly V588F (8), and may be associated with higher rates of recolonization after efforts to eradicate *S. aureus* carriage (9).

Mupirocin susceptibility often is not tested as part of routine clinical care because high-level mupirocin resistance has been reported to be relatively rare, ranging from 1% to 5% of MRSA isolates from hospitalized adult populations in North America and Europe (9–12). However, prevalences of 13% of MRSA isolates (13) and 45% of *S. aureus* isolates have been reported in single-center studies (9, 14). In the few studies that have examined rates of mupirocin resistance in children, the prevalence has ranged from 2% to 15% (15–17).

Several studies have linked mupirocin resistance to mupirocin use. A 20-year analysis of MRSA blood culture isolates in Europe found mupirocin resistance to be associated with increased use (18). In another study, decreased clinical usage of mupirocin over 5 years at a French hospital mirrored a decrease in resistance rates

(19). A case-control study by Caffrey et al. revealed a strong association between previous mupirocin exposure and subsequent mupirocin resistance in MRSA (20).

Mupirocin resistance may also aid in the spread of multidrug resistance through coselection with other resistance genes. For instance, high rates of clindamycin resistance have been observed in MupRSA isolates (7, 16). Cadilla et al. found an association between strains of mupirocin-resistant MRSA and resistance to three or more non-beta-lactam antimicrobial classes (21). Mupirocin-resistant MRSA strains isolated from several hospitals in Korea were also resistant to ciprofloxacin, clindamycin, and tetracycline (22).

To determine the prevalence of mupirocin resistance and its associated risk factors in our pediatric population, we retrospectively reviewed all skin cultures from the Division of Pediatric Dermatology that were positive for *S. aureus* at our center over a 16-month period.

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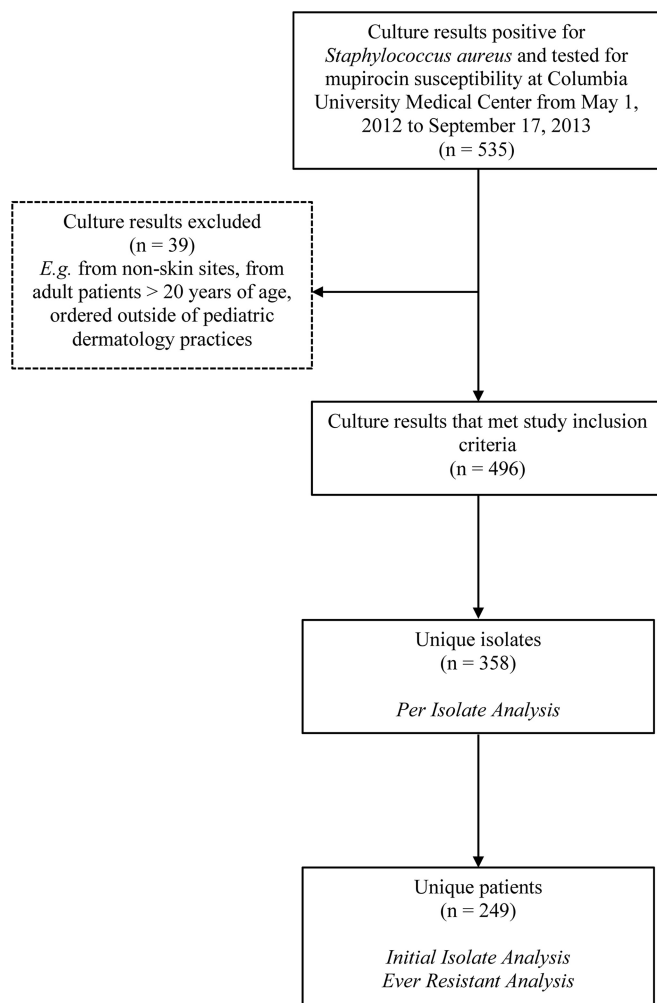


FIG 1 Flowchart summarizing the study design.

MATERIALS AND METHODS

Following institutional review board approval, the computer database of the Clinical Microbiology Laboratory at Columbia University Medical Center was queried for all culture results positive for *S. aureus* and tested for susceptibility to mupirocin during the 16-month period from 1 May 2012 to 17 September 2013. In our pediatric dermatology practice, mupirocin sensitivity testing of *S. aureus* isolates is routinely requested, and 91.4% of *S. aureus* cultures obtained during the study period were tested for mupirocin susceptibility. Outside our dermatology clinic, mupirocin susceptibility testing was not routine, which limited our study population to children seen by pediatric dermatologists.

A list of 535 individual culture results (isolates) was generated. We excluded culture results from nonskin sites (e.g., blood culture) or adults (>20 years old) and cultures not sent by physicians from our division. Isolates were obtained from sites of suspected infection and colonization. Thirty-nine culture results were excluded, resulting in 496 specimens from 249 patients (Fig. 1). Isolates obtained from the same patient on the same date with equivalent antibiotic susceptibility profiles (beta-lactams, clindamycin, daptomycin, erythromycin, levofloxacin, linezolid, trimethoprim-sulfamethoxazole, rifampin, tetracycline, vancomycin, and mupirocin) were assumed to be the same isolate. Isolates from different dates and/or isolates showing variability in susceptibility to one or more of the routinely tested antibiotics were regarded, for our analyses, as different or uniquely isolates. The 496 skin culture isolates were grouped together

by these criteria, resulting in 358 unique isolates from 249 patients. Fifty-seven patients had more than one unique isolate identified at the time of initial culture or on different visit dates; 35 patients had 2 unique isolates, and 22 patients had 3 or more unique isolates. Forty-two patients were cultured on more than one visit date.

The clinical records of all patients whose cultures met the inclusion criteria were reviewed for demographic and clinical information, including patient age, gender, zip code, primary dermatologic diagnosis, additional dermatologic diagnoses if applicable, immunosuppression, visit status, and documented history and timing of mupirocin use. Among the subset of immunosuppressed patients, conditions included solid-organ transplant, leukemia, graft-versus-host disease, severe atopic dermatitis (AD), severe granulomatous colitis, and primary immune deficiency; 7 patients were receiving therapy with a cytotoxic agent (e.g., mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, or mercaptopurine) and/or systemic steroids. Cultures obtained from patients in the emergency department were considered outpatient. Patient zip codes were grouped into five geographic regions: Mid- and Lower Manhattan (10002 to 10025; 10065 to 10282); Brooklyn, Queens, Long Island, and Staten Island (10306 to 10309; 11040 to 11787); Upper Manhattan and the Bronx (10026 to 10040; 10451 to 10472); Connecticut and Northern New York State (06831 to 06870; 10512 to 10977; 12508 to 12589); and New Jersey (07003 to 08854). Three zip codes were outside this area and were excluded from the statistical analysis of geography. Groups were selected based on borough and state boundaries; however, Upper Manhattan was included with the Bronx due to prior work suggesting these areas may be demographically and epidemiologically linked (23). Primary dermatologic diagnoses, defined as the reason the culture was sent and determined by chart review, were classified into six categories: atopic dermatitis (group 1); dermatitis not otherwise specified (NOS) (group 2); impetigo (group 3); folliculitis, pustulosis, furunculosis, or abscess (group 4); epidermolysis bullosa (EB) (group 5); and other (group 6). Group 6 included other diagnoses, such as molluscum, skin ulcer, erythema, and paronychia.

Culture result details were recorded, including body site(s), quantity of bacterial growth (classified as few, moderate, or many), presence of additional bacterial species other than *S. aureus* on the culture result (additional strains), susceptibility to a panel of routinely tested antibiotics, and mupirocin susceptibility, including the quantitative MIC. Body sites were grouped into five broad categories: head, nares, trunk, extremity (shoulders, arms, hands, hips, buttocks, legs, and feet), and skin fold (neck, axilla, perianal, inguinal and genital areas, umbilicus, popliteal fossa, and antecubital fossa). A unique isolate may have been obtained from multiple body sites from a patient during a clinic visit, and as such, body site categories were not mutually exclusive in our analysis. Mupirocin resistance was characterized as a binary outcome variable, with a MIC of <8 $\mu\text{g}/\text{ml}$ regarded as susceptible and a MIC of $\geq 8 \mu\text{g}/\text{ml}$ as resistant.

We organized the data in three different ways for statistical analysis. First, the “per-isolate” analysis included all 358 unique isolates. In this analysis, each patient may have been represented more than once due to inclusion of isolates from more than one visit. Second, the “initial-isolate” analysis included a single isolate from the first culture date collected from each patient during the study time period. Third, the “ever-resistant” analysis included a single isolate for each patient on the visit when mupirocin resistance was first, if ever, recorded or from the initial culture date if mupirocin resistance was never recorded. The initial-isolate and ever-resistant analyses included 249 separate observations, 1 for each individual patient.

For all analyses, both simple and multiple logistic regression models were fitted. Logistic regression models for per-isolate analysis included a correction for the effect of subjects having multiple samples. Briefly, if the correlation between the isolates from the same patient is r and that patient has m isolates, then the effective sample size from that patient that contributes to the final estimates is $m/(1+r)$. To perform variable selection for the multiple logistic regression model, a backward elimination ap-

proach was used, where 0.1 was the threshold for keeping a variable in the model. Statistical analysis was performed using SAS 9.3 and R.

RESULTS

A total of 358 unique isolates and 249 individual patients were included in this retrospective study, with an average initial age of 5.4 (range, 0 to 19.2) years; 53.8% were male, and 46.2% were female, with the largest percentage of patients residing in Upper Manhattan and the Bronx (30.1% of patients) (see Table S1 in the supplemental material).

At the time of initial culture, 35.3% of the patients with *S. aureus* infection had a documented clinical history of prior mupirocin use. A large proportion (55.4%) of patients carried a diagnosis of atopic dermatitis. The most common primary dermatologic diagnosis (i.e., the clinical reason a skin culture was obtained) on the day of culture was atopic dermatitis, accounting for 36.6% of patients at initial culture, followed by dermatitis NOS (16.5%), impetigo (14.9%), folliculitis/pustulosis and abscess (14.1%), and EB (6.4%). The majority of initial cultures were performed in the outpatient setting (96.0%) in a non-immunosuppressed (96.4%) group of patients (see Table S1 in the supplemental material).

For all 358 unique isolates, the overall prevalence of mupirocin resistance was 31.3%. The majority of isolates (96 of 112; 85.7%) carried high-level resistance, with MICs of $\geq 1,024$ $\mu\text{g/ml}$. Sixteen isolates (14.3%) were classified as having low-level resistance, with MICs ranging from 8 to 64 $\mu\text{g/ml}$. Two hundred ninety-three isolates (81.8%) were methicillin-susceptible *S. aureus* (MSSA), and 65 (18.2%) were MRSA, in line with MRSA rates from other pediatric populations (24, 25); 19.3% of patients had a mupirocin-resistant isolate on their first culture in the study period, and 22.1% had at least one culture that was mupirocin resistant over the study period.

The results of univariate logistic regression of the per-isolate, initial-isolate, and ever-resistant analyses identified many of the same risk factors, including prior mupirocin use, atopic dermatitis, immunosuppression, and MRSA, among which only a history of prior mupirocin use was found to be a significant risk factor for all three in multivariate analysis (Tables 1 and 2; see Table S1 in the supplemental material). However, atopic dermatitis, immunosuppression, and inpatient status were found to be significant in 2 out of 3 multivariate analyses.

There were also significant differences between zip code groups (ZCG). ZCG 1, which included Mid- and Lower Manhattan, had the least mupirocin resistance (8.3%) and was used as the reference group. In per-isolate and ever-resistant univariate analyses, ZCG 3, which comprises Upper Manhattan and the Bronx, had significantly more mupirocin resistance (Tables 1 and 2). Multivariate analysis of the ever-resistant data set also highlighted ZCG 3 (Table 2).

Significant differences were also identified between primary-diagnosis groups. For all three data analyses, patients with a diagnosis of dermatitis NOS were less likely than patients with atopic dermatitis to have mupirocin-resistant isolates, whereas those of patients with EB were more likely to be mupirocin resistant (Tables 1 and 2; see Table S1 in the supplemental material).

Isolates from patients with AD were more likely to be oxacillin resistant (i.e., MRSA) and mupirocin resistant than isolates from nonatopic children. Of the MRSA isolates in this study, 67.7% were found in patients with AD. The majority of MRSA isolates

(68.2%) in patients with AD were resistant to mupirocin compared to only 28.6% of MRSA isolates in nonatopic patients.

Forty-two subjects had cultures obtained on more than one date during the study period. Not unexpectedly, in 19 subjects with MupRSA isolates (7 of which were MRSA), colonization persisted despite the use of mupirocin. In six subjects initially found to have mupirocin-sensitive MSSA on culture, a subsequent isolate was found to be mupirocin resistant; all 6 patients had a history of mupirocin use prior to repeat cultures. In contrast, we never observed conversion to mupirocin resistance in the absence of mupirocin use. There were no instances where exposure to mupirocin preceded the acquisition of MRSA.

DISCUSSION

A study period prevalence of 31.3% MupRSA is one of the highest reported to date, and it is alarming that 22.1% of the children had a mupirocin-resistant isolate at some time during the study period. Other studies in pediatric populations have found various rates of mupirocin resistance, including 1.8% in initial MRSA isolates from a predominantly outpatient setting in the northwest United States (15), 14.7% in *S. aureus* isolates from children with recurrent skin and soft tissue infections seen at a tertiary care center in Houston, TX (16), and 9.8% in *S. aureus* isolates from a mixed group of children with single or recurrent skin and soft tissue infections from the same center in Houston (17). In adult populations, the prevalence of mupirocin resistance reported is low, generally ranging from 1 to 5% (7, 9–12, 26). The highest rate reported was 45% in clinical staphylococcal isolates from patients at a Turkish hospital (14).

We found a strong association between mupirocin resistance and prior mupirocin use in all three analyses (odds ratio [OR] = 19.2 to 26.5; $P < 0.001$), supporting the notion that use of mupirocin may be the primary driver of resistance. This is consistent with previous reports, including a case-control study revealing a strong association (OR = 9.8) between previous mupirocin exposure and subsequent resistance in MRSA (20) and several observational studies (18, 19). A recent study in a pediatric population in Texas also reported an association between previous mupirocin use and mupirocin resistance (17).

Mupirocin resistance was highly prevalent in our MRSA isolates (55.4%), and MRSA was a strong risk factor for resistance to mupirocin. This finding agrees with studies in adult populations (27, 28), where mupirocin resistance was found more frequently in MRSA than MSSA, but contrasts with a recent study in children (8.3% and 21.4% [MRSA:MSSA]) (16). The association between levofloxacin and mupirocin resistance (OR = 3.6; $P = 0.006$) in univariate but not in multivariate analysis may be related to the fact that levofloxacin resistance is more common in MRSA (29). Over three-quarters (39/51) of levofloxacin-resistant isolates in our study were MRSA. We did not see an association between mupirocin resistance and clindamycin resistance, as has been reported previously (7).

Although our study was not designed to examine longitudinal factors influencing the emergence and persistence of mupirocin resistance, the patterns observed in patients with multiple isolates may give some insight into this process. There were multiple instances where mupirocin treatment failed to eradicate MupRSA isolates and where a MupRSA isolate replaced a mupirocin-sensitive *S. aureus* (MupSSA) isolate after treatment with mupirocin,

TABLE 1 Per-isolate analysis

Parameter	Total [n (%)]	No. (%) mupirocin susceptible (n = 246) ^a	No. (%) mupirocin resistant (n = 112)	Univariate OR (95% CI) ^b	P value	Multivariate OR ^c (95% CI)	P value
Demographic factors^a							
Female sex	170 (47.49)	109 (44.31)	61 (54.46)	1.503 (0.727–3.111)	0.272		
Additional dermatologic diagnosis	126 (35.20)	82 (33.33)	44 (39.29)	1.294 (0.661–2.533)	0.452		
Atopic dermatitis	225 (62.85)	139 (56.50)	86 (76.79)	2.546 (1.274–5.088)	0.008	4.906 (1.435–16.778)	0.011
Immunosuppression	30 (8.40)	8 (3.27)	22 (19.64)	7.242 (2.899–18.089)	<0.001	7.166 (2.613–19.651)	<0.001
History of mupirocin use	185 (51.68)	81 (32.93)	104 (92.86)	26.482 (11.197–62.631)	<0.001	29.128 (10.819–78.421)	<0.001
Outpatient	339 (94.69)	237 (96.34)	102 (91.07)	0.387 (0.156–0.961)	0.041		
Zip code group							
Mid- and Lower Manhattan (ZCG 1)	60 (16.76)	52 (21.14)	8 (7.14)	1			
Brooklyn, Queens, Long Island, and Staten Island (ZCG 2)	69 (19.27)	40 (16.26)	29 (25.89)	4.713 (1.073–20.701)	0.04		
Upper Manhattan and the Bronx (ZCG 3)	124 (34.64)	75 (30.49)	49 (43.75)	4.247 (1.158–15.579)	0.029		
Connecticut and northern New York State (ZCG 4)	47 (13.13)	35 (14.23)	12 (10.71)	2.229 (0.557–8.916)	0.257		
New Jersey (ZCG 5)	55 (15.36)	41 (16.67)	14 (12.50)	2.220 (0.543–9.068)	0.267		
Primary diagnosis							
Atopic dermatitis (group 1)	144 (40.22)	88 (35.77)	56 (50.00)	1		1	
Dermatitis NOS (group 2)	46 (12.85)	43 (17.48)	3 (2.68)	0.110 (0.023–0.529)	0.006	0.283 (0.067–1.206)	0.088
Impetigo (group 3)	48 (13.41)	36 (14.63)	12 (10.71)	0.524 (0.237–1.159)	0.111	1.059 (0.295–3.795)	0.93
Folliculitis, pustulosis, abscess (group 4)	58 (16.20)	38 (15.45)	20 (17.68)	0.827 (0.372–1.837)	0.641	0.576 (0.204–1.625)	0.298
Epidermolysis bullosa (group 5)	28 (7.82)	10 (4.07)	18 (16.07)	2.829 (1.051–7.611)	0.04	5.567 (1.088–28.482)	0.039
Other (group 6)	34 (9.50)	31 (12.60)	3 (2.68)	0.152 (0.046–0.505)	0.002	0.376 (0.095–1.493)	0.164
Culture site							
Head	94 (26.40)	69 (28.05)	25 (22.73)	0.755 (0.432–1.318)	0.322		
Nares	49 (13.76)	27 (10.98)	22 (20.00)	2.028 (1.098–3.744)	0.024		
Trunk	30 (8.43)	19 (7.72)	11 (10.00)	1.328 (0.602–2.928)	0.483		
Extremity	165 (46.35)	103 (41.87)	62 (56.36)	1.793 (1.129–2.848)	0.013		
Skin fold	112 (31.46)	80 (32.52)	32 (29.09)	0.851 (0.501–1.446)	0.552		
Unspecified	6 (1.69)	5 (2.03)	1 (0.91)	0.442 (0.050–3.898)	0.462		
Strain characteristics							
MRSA	65 (18.16)	29 (11.79)	36 (32.14)	3.545 (1.576–7.970)	0.002		
Additional strain(s)	41 (11.45)	28 (11.38)	13 (11.61)	1.022 (0.441–2.369)	0.959		
Antibiotic resistance							
Amoxicillin	3 (1.02)	1 (0.46)	2 (2.60)	5.760 (0.524–63.367)	0.152		
Clindamycin	90 (25.49)	60 (24.80)	30 (27.03)	1.124 (0.625–2.020)	0.697		
Erythromycin	153 (42.86)	97 (39.43)	56 (50.45)	1.564 (0.818–2.991)	0.176	2.054 (0.938–4.499)	0.072
Levofloxacin	51 (14.24)	22 (8.95)	29 (25.90)	3.558 (1.433–8.833)	0.006		
Oxacillin	65 (18.16)	29 (11.79)	36 (32.14)	3.545 (1.576–7.970)	0.002		
Rifampin	6 (1.68)	3 (1.22)	3 (2.68)	2.229 (0.498–9.989)	0.295		
Trimethoprim-sulfamethoxazole	4 (1.12)	1 (0.41)	3 (2.68)	6.743 (0.576–78.942)	0.128		
Tetracycline	44 (12.29)	30 (12.20)	14 (12.50)	1.029 (0.300–3.527)	0.964		
Amt of bacterial growth							
Few	98 (28.32)	80 (33.33)	18 (16.98)	1		1	
Moderate	157 (45.38)	102 (42.50)	55 (51.89)	2.397 (1.334–4.304)	0.003	3.327 (1.486–7.446)	0.004
Many	91 (26.30)	58 (24.17)	33 (31.13)	2.529 (1.190–5.376)	0.016	2.271 (0.932–5.534)	0.071

^a The mean ages were 5.00 years (mupirocin-susceptible group) and 8.21 years (mupirocin-resistant group); univariate OR (95% CI), 1.136 (1.066–1.210); $P < 0.001$.

^b CI, confidence interval.

^c For the multivariate analysis, variables trimmed from the backward model selection are excluded, and only variables selected for the final model are shown.

showing that mupirocin eradication strategies may fail in multiple ways.

Place of residence was associated with mupirocin resistance, suggesting that geographic or socioeconomic factors may contribute to the development of resistance. Compared to the reference ZCG 1 (Mid- and Lower Manhattan), patients from ZCG 3 (Har-

lem, Washington Heights, Inwood, and the Bronx) were more likely to carry MupRSA, indicating that there may be geographic pockets of higher/lower mupirocin resistance in the greater New York City area. This pattern may be due to factors such as transmission rates, population density, prescribing patterns, or higher MRSA prevalence. Indeed, we found higher rates of MRSA in ZCG

TABLE 2 Ever-resistant analysis

Parameter	Total [n (%)]	No. (%) mupirocin susceptible (n = 194)	No. (%) mupirocin resistant (n = 55)	Univariate OR (95% CI) ^b	P value	Multivariate OR ^c (95% CI)	P value
Demographic factors^a							
Female sex	115 (46.18)	88 (45.36)	27 (49.09)	1.162 (0.638–2.115)	0.624		
Additional dermatologic diagnosis	79 (31.73)	60 (30.93)	19 (34.55)	1.179 (0.625–2.221)	0.611		
Atopic dermatitis	138 (55.42)	100 (51.55)	38 (69.09)	2.101 (1.111–3.975)	0.022	11.454 (1.986–66.066)	0.006
Immunosuppression	9 (3.63)	4 (2.07)	5 (9.09)	4.725 (1.223–18.249)	0.024	17.142 (1.302–225.727)	0.031
History of mupirocin use	89 (35.74)	41 (21.13)	48 (87.27)	25.589 (10.778–60.752)	<0.001	51.571 (13.720–193.841)	<0.001
Outpatient	238 (95.58)	188 (96.91)	50 (90.91)	0.319 (0.094–1.089)	0.068	0.087 (0.011–0.663)	0.018
Zip code group							
Mid- and Lower Manhattan (ZCG 1)	51 (20.48)	47 (24.23)	4 (7.27)	1		1	
Brooklyn, Queens, Long Island, and Staten Island (ZCG 2)	42 (16.87)	32 (16.49)	10 (18.18)	3.672 (1.059–12.733)	0.04	1.277 (0.218–7.490)	0.787
Upper Manhattan and the Bronx (ZCG 3)	75 (30.12)	53 (27.32)	22 (40.00)	4.877 (1.567–15.181)	0.006	7.971 (1.555–40.851)	0.013
Connecticut and Northern New York State (ZCG 4)	37 (14.86)	27 (13.92)	10 (18.18)	4.352 (1.244–15.226)	0.021	4.201 (0.756–23.343)	0.101
New Jersey (ZCG 5)	41 (16.47)	32 (16.49)	9 (16.36)	3.305 (0.937–11.657)	0.063	3.065 (0.494–19.030)	0.229
Primary diagnosis							
Atopic dermatitis (group 1)	92 (36.95)	66 (34.02)	26 (47.27)	1		1	
Dermatitis NOS (group 2)	42 (16.87)	40 (20.62)	2 (3.64)	0.127 (0.029–0.564)	0.007	0.506 (0.049–5.201)	0.567
Impetigo (group 3)	36 (14.46)	30 (15.46)	6 (10.91)	0.508 (0.189–1.362)	0.178	1.844 (0.336–10.115)	0.481
Folliculitis, pustulosis, abscess (group 4)	34 (13.65)	26 (13.40)	8 (14.55)	0.781 (0.313–1.947)	0.596	1.035 (0.216–4.961)	0.966
Epidermolysis bullosa (group 5)	16 (6.43)	5 (2.58)	11 (20.00)	5.585 (1.768–17.645)	0.003	13.037 (1.468–115.739)	0.021
Other (group 6)	29 (11.65)	27 (13.92)	2 (3.64)	0.188 (0.042–0.848)	0.03	0.170 (0.010–2.849)	0.218
Culture site							
Head	69 (27.71)	58 (29.90)	11 (20.00)	0.586 (0.283–1.215)	0.151		
Nares	36 (14.46)	22 (11.34)	14 (25.45)	2.670 (1.259–5.661)	0.01		
Trunk	19 (7.63)	14 (7.22)	5 (9.09)	1.286 (0.442–3.741)	0.645		
Extremity	106 (42.57)	74 (38.14)	32 (58.18)	2.256 (1.227–4.149)	0.009	2.782 (0.967–8.003)	0.058
Skin fold	90 (36.14)	69 (35.57)	21 (38.18)	1.119 (0.603–2.077)	0.722		
Unspecified	5 (2.01)	4 (2.06)	1 (1.82)	0.880 (0.096–8.035)	0.91		
Strain characteristics							
MRSA	36	21 (10.82)	15 (27.27)	3.089 (1.464–6.517)	0.003		
Additional strain(s)	31 (12.45)	23 (11.86)	8 (14.55)	1.265 (0.532–3.011)	0.594		
Amt of bacterial growth							
Few	72 (29.88)	63 (33.33)	9 (17.31)	1		1	
Moderate	109 (45.23)	82 (43.39)	27 (51.92)	2.305 (1.012–5.248)	0.047	4.030 (1.122–14.475)	0.033
Many	60 (24.90)	44 (23.28)	16 (30.77)	2.545 (1.032–6.279)	0.043	1.699 (0.430–6.721)	0.45

^a The mean ages were 4.77 years (mupirocin-susceptible group) and 7.86 years (mupirocin-resistant group); univariate OR (95% CI), 1.123 (1.060–1.190; $P < 0.001$; $n = 249$).

^b CI, confidence interval.

^c For the multivariate analysis, variables trimmed from the backward model selection are excluded, and only variables selected for the final model are shown.

3 (18.5%) than in ZCG 1 (11.7%). A recent study found a high incidence of intrahousehold *S. aureus* transmission in northern Manhattan (similar to ZCG 3) and demonstrated that environmental contamination with a colonizing or clinical infection strain was associated with transmission (30). Mupirocin resistance may also vary on a broader geographic scale. A large multi-center study found generally low rates of mupirocin resistance in *S. aureus* isolates from outpatient dermatology centers across the United States, with the exception of 33.9% at a center in Florida (31).

The strong association between MupRSA and diseases such as AD and EB is in agreement with prior studies (17, 32) and is likely due at least in part to the increased use of antibiotics in these patients. It is also likely that high cutaneous bacterial burdens (33–35), more frequent infection, and the inability to eradicate *S.*

aureus lead to a higher probability of acquiring a persistent MupRSA strain.

There are several limitations to this study. It is likely that patients presenting to dermatology at a tertiary care center represent a more severely and/or chronically infected population. These patients may be more likely to be exposed to antibiotics and less likely to clear infection, resulting in higher rates of MupRSA than in the general population. More severely infected patients may have been overrepresented because they were seen more often in follow-up. Indeed, culture results from patients with MupRSA do appear to be overrepresented in our per-isolate data, but this did not seem to significantly affect our analysis of risk factors, which were similar in all three analyses. A review of pediatric-dermatology cultures obtained over the study period revealed that 8.6% of the cultures were not tested for mupirocin resistance for a variety

of logistical reasons, and as cultures are not routinely held after processing, we were unable to retrospectively obtain mupirocin sensitivity for these isolates. While we cannot rule out a bias in isolate selection, the small percentage of untested isolates suggests that this may not have had a significant impact on our analysis.

Mupirocin is an important component of antimicrobial therapy that is recommended by the Infectious Disease Society of America (IDSA) for treatment of children with minor skin infections caused by MRSA or neonatal pustulosis and for decolonization of patients with recurrent MRSA skin and soft tissue infections (36). Prophylactic intranasal mupirocin has been shown to decrease rates of nosocomial *S. aureus* infection in carriers (37). A recent multicenter study found a significant decrease in intensive care unit bloodstream infections when universal intranasal mupirocin and chlorhexidine washes were employed as a decolonization strategy (38). It is unclear what the impact of very high rates of MupRSA would have been in these studies, but one may speculate that the strategies may have been less successful. Furthermore, in situations where rates of mupirocin resistance in MRSA are high, it is possible that indiscriminate mupirocin use could lead to co-selection of methicillin-resistant strains. Presently, it seems prudent to test for mupirocin susceptibility in patients with a history of mupirocin use, culture-positive MRSA, or atopic dermatitis and in those patients who are immune suppressed or hospitalized. Judicious clinical use of mupirocin, particularly in high-risk populations, may prevent the development of additional and widespread resistance. Going forward, it will be critical to identify and validate the efficacies of alternative topical strategies.

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