2010

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Citation/Publisher Attribution

Caffrey, A. R., Quilliam, B. J., & LaPlante, K. L. (2010). Risk Factors Associated With Mupirocin Resistance in Meticillan-Resistant *Staphylococcus aureus*. *Journal of Hospital Infection*, *76*(3), 206-210. doi: 10.1016/j.jhin.2010.06.023
Available at: http://dx.doi.org/10.1016/j.jhin.2010.06.023

Risk Factors Associated with Mupirocin Resistance in Methicillin-Resistant Staphylococcus aureus

Original Article: Risk factors associated with mupirocin resistance in methicillin-resistant *Staphylococcus aureus*

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Running Title: Risk factors of mupirocin-resistant MRSA

This work was presented in part as a slide session at the 49th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Francisco, CA on September 13, 2009.

Summary

Implementation of methicillin-resistant *Staphylococcus aureus* (MRSA) decolonization programs has been increasing and the emergence of mupirocin resistance has been reported. However, the patient level risk factors associated with mupirocin resistance are not clear. We identified independent predictors of mupirocin resistance in MRSA among Providence Veterans Affairs Medical Center patients with MRSA positive culture dates between July 1, 2004 and June 30, 2008 using a frequency matched case-control study. Forty cases (mupirocin-resistant) were matched on culture date quarter and year to 270 controls (mupirocin susceptible). The adjusted conditional logistic regression model identified three significant independent predictors associated with mupirocin resistance in MRSA: 1) exposure to mupirocin in the year prior to the culture date (odds ratio [OR] 9.84, 95% confidence interval [CI] 2.93-33.09), 2) *Pseudomonas aeruginosa* infection in the year before the culture-related admission (OR 4.85, 95% CI 1.20-19.61), and 3) cefepime utilization in the year prior to culture (OR 2.80, 95% CI 1.03-7.58). In sensitivity analyses, previous mupirocin exposure was associated with low-level (minimum inhibitory concentrations [MICs] 8–128 mg/L; 23 cases, 202 controls; OR 6.32, 95% CI 1.58-25.33) and high-level (MICs ≥256 mg/L; 17 cases, 151 controls; OR 11.18, 95% CI 1.89-66.30) mupirocin resistance. To our knowledge, this is the first case-control study to reveal a strong association between previous mupirocin exposure and subsequent mupirocin resistance in MRSA, with demonstrated robustness in low and high-level mupirocin resistance. Mupirocin susceptibility monitoring is critical for facilities instituting decolonization with mupirocin as increased utilization may reduce effectiveness through resistance.

Keywords: methicillin-resistant *Staphylococcus aureus*, mupirocin resistance, risk factors

Introduction

Despite the implementation of evidence-based infection control practices, methicillin-resistant *Staphylococcus aureus* (MRSA) infection and colonization rates continue to increase, contributing to escalating healthcare costs.[1-4] Decolonization regimens, including the eradication of MRSA carriage with topical antimicrobial and antiseptic agents, have been used variably in the clinical setting.[4, 5] Mupirocin has been the mainstay of decolonization therapy as it is the only topical antibiotic approved for the eradication of MRSA nares colonization in the United States.[6] However, decolonization with mupirocin remains controversial as eradication appears to be short-term, is not achieved in all patients, and does not consistently prevent subsequent infections.[7-11]

Mupirocin resistance emerged shortly after this topical antibiotic was introduced into clinical practice, thus affecting the efficacy and effectiveness of mupirocin.[8, 9, 12-14] A plasma-mediated *mupA* gene appears to be associated with high-level resistance, while low-level resistance is associated with chromosomal point mutations.[6, 15-17] Data collected from susceptibility monitoring can be used to discern the population subgroups at the highest risk for mupirocin-resistant MRSA as no common risk factors have been identified from the limited research conducted to date.[18-21] It was therefore the intent of this study to identify independent predictors associated with mupirocin-resistant MRSA among our Veterans Affairs Medical Center (VAMC) patients in Providence, Rhode Island, United States.

Methods

Study setting and data sources

Routine mupirocin susceptibility testing of MRSA isolates was initiated in June of 2004 at the Providence VAMC, a 119-bed hospital with 32 subspecialty clinics. The Infectious Diseases Research Laboratory assessed each patient's first unique MRSA isolate from any culture site within a calendar year for mupirocin resistance using E-tests (AB Biodisk, Solna, Sweden) to determine minimum inhibitory concentrations (MICs). For these analyses, mupirocin susceptibility results were combined with inpatient and outpatient data extractions from standardized databases and electronic medical records. This study was reviewed and approved by the Institutional Review Boards of the Providence VAMC and University of Rhode Island, and the Providence VAMC Research and Development Committee.

Patient population and study design

Our retrospective pharmacoepidemiologic study utilized a case-control design. Adults with MRSA positive culture dates between July 1, 2004 and June 30, 2008 were selected for inclusion. Amongst this eligible population, we identified two groups of patients, those with mupirocin-resistant (cases) and susceptible (controls) isolates. Resistance included both low (8–128 mg/L) and high-level (≥256 mg/L) MICs as each has been associated with therapy failure.[8, 9, 13, 14, 22] We categorized isolates with MICs less than or equal to 4 mg/L as susceptible and selected the first MRSA positive isolate, identified by the earliest culture date during the study period, for inclusion. We employed case-base sampling to select controls with susceptible

isolates from the source population. Cases were frequency matched with controls on culture date, randomly selecting up to 10 controls per case within strata of culture date quarter and year (16 quarters over four years).

Independent predictors

The potential predictors assessed included patient demographics and comorbid conditions, as well as healthcare and antibiotic exposures. We utilized International Classification of Diseases, Ninth Edition (ICD-9) diagnosis and procedure codes associated with inpatient admissions and outpatient visits to identify patient comorbidities, including site-specific and organism-specific infections, in the year prior to admission. As the relevant exposure window for mupirocin resistance is not well-defined, we evaluated inpatient admissions and surgeries in two non-mutually exclusive time periods (90 days and one year) prior to the culture-related admission. We manually reviewed all microbiology results from electronic medical records to determine whether patients were colonized, infected, or concomitantly colonized and infected with MRSA. Antibiotic exposures in the 90 days prior to the culture date (recent past) and in the previous year were assessed from inpatient and outpatient prescription records. We evaluated cephalosporins by generation (i.e. 1^{st}, 2^{nd}, 3^{rd}, and 4^{th}) separately from other beta-lactams as an association between third-generation cephalosporins and low-level mupirocin resistance has been reported.[21]

Statistical analysis

We assessed between-group differences by case-control status using a χ^2 or Fisher's exact test as appropriate for categorical covariates and the Mann-Whitney U test for non-normally distributed continuous variables. In multivariable modeling, a manual, non-computer generated backward elimination approach was implemented to identify independent predictors associated with mupirocin resistance.[23] Model development was guided by likelihood ratio tests, Wald statistics, and parameter coefficients.[23] We estimated crude and adjusted odds ratios, including their respective 95% confidence intervals, with conditional logistic regression. In sensitivity analyses, the predictors we identified in the primary analysis were evaluated separately for low and high-level mupirocin resistance. All statistical tests were conducted with a two-tailed alpha and all analyses were performed using SAS (SAS Institute Inc., Cary, NC, Version 9.1.3).

Results

Among Providence VAMC patients, 40 cases with mupirocin-resistant MRSA isolates were identified during the study period. The average number of cases per quarter was three (40 cases in 12 quarters). All cases were successfully matched to 270 controls, of the available 369 patients with mupirocin susceptible MRSA positive isolates, based on culture date quarter and year. Each case had between three and ten matched controls (mean 7). Surgical procedures, chronic skin ulcers, and *Pseudomonas aeruginosa* (*P. aeruginosa*) infections were more common among mupirocin-resistant MRSA cases compared to susceptible controls in the year prior to the culture-related admission. No other significant variations in demographics, comorbid conditions, and healthcare exposures were observed by case-control status, as illustrated in Tables I and II. While antibiotic utilization was assessed in the 90 days before the culture date, univariate

likelihood ratio testing identified inpatient and outpatient exposures during the previous year to be more significant. Fluoroquinolones were the most commonly prescribed antibiotic class among cases and controls, as detailed in Table III. Cases were exposed to mupirocin, vancomycin, and cefepime more often than controls.

The adjusted conditional logistic regression model identified three independent predictors associated with mupirocin-resistant MRSA, as presented in Table IV. Mupirocin resistance was 9.84 times more likely among patients exposed to mupirocin in the year prior to the culture date compared to those with no such antibiotic exposure. The site of previous mupirocin exposure (7/17 nares, 10/17 skin) did not vary by case-control status. Mupirocin exposures occurred in the outpatient (5/7 cases, 8/10 controls) and inpatient (4/7 cases, 5/10 controls) settings (includes multiple therapy episodes). Among patients exposed in the outpatient setting for nares decolonization, 83% (5/6) were treated preoperatively. There were no significant differences in length of previous mupirocin exposure by case-control status.

Additionally, previous treatment with cefepime, a fourth-generation cephalosporin, was independently associated with mupirocin resistance. The mean length of prior cefepime therapy did not differ significantly between cases and controls. MRSA isolates from patients infected with *P. aeruginosa* in the year before the culture-related admission were 4.85 times more likely to display mupirocin resistance as compared to cultures from patients without a history of this infection type. Sensitivity analyses (Table IV) substantiated previous mupirocin exposure as an independent predictor of low-level (23 cases, 202 controls) and high-level (17 cases, 151

controls) mupirocin resistance, while the association with previous *P. aeruginosa* infection was only observed in low-level resistance.

Discussion

To our knowledge, this is the first published case-control study to reveal a strong association between previous mupirocin exposure and subsequent mupirocin resistance in MRSA, with demonstrated robustness in low and high-level mupirocin resistance. While the selective pressure of antibiotics intuitively affects the development of resistance and several researchers have ecologically attributed increased mupirocin resistance to escalated mupirocin utilization, formal analytic comparisons had yet to substantiate this hypothesis at the patient-level.[13, 18, 19, 21, 24, 25] In a placebo-controlled trial, exposure to mupirocin before randomization was not associated with resistance (RR 1.52, 95% CI 0.71-3.27).[13] Further, mupirocin therapy was not predictive of resistance in a case-control study conducted among patients from the VAMC in Mountain Home, Tennessee (OR 1.64, 95% CI 0.77-3.53).[18] Despite this finding, rising high-level resistance rates at the Mountain Home VAMC coincided with increased facility-level mupirocin use over the study period and a decline in resistance was later observed among inpatient non-nares MRSA isolates after restrictions were placed on mupirocin prescribing practices.[18, 25]

In our study, we identified previous *P. aeruginosa* infections and prior utilization of cefepime to be independent predictors of mupirocin resistance, although the reasons for the observed associations are less apparent. Mupirocin is an antibiotic produced by the gram-negative bacteria *Pseudomonas fluorescens*. As such, *Pseudomonas* is insensitive to mupirocin

resulting from its inherent resistance to the antibiotic it produces.[26, 27] The *mupA* gene, which exists in both low and high-level resistance, is unstable and the movement of *mupA*-mediated mupirocin resistance between plasmids exists between bacterial isolates.[28-30] It is currently unknown if *P. aeruginosa* is a carrier and potentially harbors the *mupA* gene complex. *P. aeruginosa* infections among cases did not vary significantly by level of mupirocin resistance, and while *Pseudomonas* was predictive of low-level resistance, the decreased sample size in sensitivity analyses likely impacted the lack of association with high-level resistance. No differences were discerned by case-control status in *P. aeruginosa* susceptibility profiles and *P. aeruginosa* infection sites (e.g. skin, urine, sputum). Perhaps the significance of this predictor relates to its opportunistic nature, affecting seriously ill patients, rather than the infecting organism itself.

Cefepime is a broad-spectrum antibiotic with activity against a number of gram-positive and gram-negative organisms.[31] Although cefepime is indicated for the treatment of *P. aeruginosa* infections, the overlap between these predictors was not significant (6/31), as confirmed by the absence of collinearity and effect modification. We did not observe patterns related to prescribing physician or underlying infection responsible for the cefepime exposure that would explain the association with mupirocin resistance. In a case-control study conducted among patients admitted to the intensive care units of a Korean hospital, antibiotics, other than cefepime and topical mupirocin, were identified as predictors of mupirocin-resistant MRSA including piperacillin-tazobactam (odds ratio [OR] 13.8, 95% confidence interval [CI] 1.8-105.0), third-generation cephalosporins (OR 5.0, 95% CI 1.6-15.5), and quinolones (OR 3.4, 95% CI 1.1-10.7).[21] These empiric exposures to antibiotics without MRSA coverage may select

for MRSA exhibiting mupirocin resistance. Or, this finding may be the result of combined patient-level factors and aggregate comorbidity burden of an underlying group of patients that was not detected by the individual covariates assessed.

The findings of this study are limited in several manners. The study sample size was small, including 40 cases with mupirocin resistance and 270 matched controls with mupirocin susceptible MRSA. While the estimated measures of association may be imprecise, the direction of the association is not affected by the small sample size, as evidenced with the consistency of the significant crude and multivariable adjusted estimates. Even at the low end of the confidence interval, mupirocin resistance is still 2.93 times more likely among those exposed to mupirocin in the year prior to culture, representing a clinically relevant increased risk. Another limitation is the lack of knowledge regarding the timing of organism acquisition. We were not able to capture the length of colonization or infection. As such, antibiotic exposures may have occurred after colonization or infection with either mupirocin susceptible or mupirocin-resistant MRSA.

Our study was also limited by the utilization of ICD-9 diagnosis codes for the identification of previous infections. The sensitivity and specificity of many organism-specific diagnosis codes, including MRSA and *Pseudomonas*, are not known. These codes may be under-utilized in comparison to site-specific infection codes. Unobserved covariates have the potential to influence the findings of any study through residual confounding. The aim of this study was not to provide evidence in support of a causal association between a specific exposure and mupirocin resistance necessitating the control of confounding factors in order to observe the true association, but rather to identify independent predictors of mupirocin resistance. Our study

findings are limited to the population served by the Providence VAMC. Only eight women were included in this study (0 cases, 8 controls), limiting the generalizability of the findings.

While few independent predictors of mupirocin resistance have been elucidated to date, we demonstrated the utility of mupirocin susceptibility monitoring for the identification of patient-level factors associated with resistance. We observed a substantial increased risk of mupirocin-resistant MRSA, including both low and high-level resistance, among patients previously exposed to mupirocin. An increased likelihood of mupirocin resistance was also noted among patients infected with *Pseudomonas* in the year before admission or treated with cefepime in the year prior to culture. Future research directions include substantiating each of these independent predictors as risk factors for mupirocin resistance, including the assessment of possible mechanisms, causal or otherwise, for these associations in risk factor analyses. Forthcoming investigations should also focus on the prognosis of patients with mupirocin resistance in terms of clinical outcomes.

Acknowledgements

We gratefully acknowledge the Center on Systems, Outcomes & Quality in Chronic Disease & Rehabilitation, HSR&D REAP, Providence VAMC, for data storage and software assistance.

The views expressed are those of the authors and do not necessarily reflect the position or policy of the United States Department of Veterans Affairs.

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Table I. Demographics and comorbid conditions among patients with mupirocin-resistant (cases) or mupirocin susceptible (controls) methicillin-resistant *Staphylococcus aureus*.

Covariates	Cases N = 40	Controls N = 270	P-value
Age (years), mean (sd)	75.6 (11.0)	72.0 (13.1)	0.12
Male gender	40 (100.0)	262 (97.0)	0.60
Race			
White	32 (80.0)	217 (80.4)	0.96
Other/unknown[a]	8 (20.0)	53 (19.6)	
Comorbid conditions			
Chronic respiratory disease[b]	21 (52.5)	110 (40.7)	0.16
Renal disease	21 (52.5)	115 (42.6)	0.24
Diabetes	20 (50.0)	108 (40.0)	0.23
Heart failure	18 (45.0)	103 (38.2)	0.41
Coronary heart disease	17 (42.5)	125 (46.3)	0.65
Cancer	9 (22.5)	68 (25.2)	0.71
Dialysis	3 (7.5)	13 (4.8)	0.44
Infections, previous year[c]			
Pneumonia[d]	14 (35.0)	62 (23.0)	0.10
Chronic skin ulcer[d]	11 (27.5)	40 (14.8)	0.04
Bacteraemia[d]	4 (10.0)	13 (4.8)	0.25
MRSA	3 (7.5)	14 (5.2)	0.47
Pseudomonas aeruginosa	5 (12.5)	5 (1.9)	<0.01

Data are no. (%), unless otherwise indicated. sd, standard deviation; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] "Other/unknown" race includes African American, Native Hawaiian/Pacific Islander, and unknown.

[b] "Chronic respiratory disease" includes chronic bronchitis, asthma, and emphysema.

[c] Infection in the year prior to admission.

[d] Attributed to any organism.

Table II. Healthcare exposures and culture characteristics among patients with mupirocin-resistant (cases) or mupirocin susceptible (controls) methicillin-resistant *Staphylococcus aureus*.

Covariates	Cases N = 40	Controls N = 270	P-value
Inpatient admission			
Previous 90 days	18 (45.0)	98 (36.3)	0.29
Previous year	28 (70.0)	166 (61.5)	0.30
Surgery			
During admission	8 (20.0)	58 (21.5)	0.83
Previous 90 days	4 (10.0)	16 (5.9)	0.31
Previous year	10 (25.0)	32 (11.9)	0.02
Admitted from home	37 (92.5)	228 (84.4)	0.23
Devices during admission[a]			
Central catheter	8 (20.0)	32 (11.9)	0.15
Urinary catheter	7 (17.5)	37 (13.7)	0.52
Mechanical ventilation	3 (7.5)	28 (10.4)	0.78
Culture site			
Nares	28 (70.0)	167 (61.9)	0.32
Tissue	5 (12.5)	29 (10.7)	0.79
Sputum	3 (7.5)	35 (13.0)	0.44
Urine	3 (7.5)	11 (4.1)	0.40
Blood	1 (2.5)	17 (6.3)	0.49
Bone	0 (0.0)	3 (1.1)	1.00
Non-specific	0 (0.0)	8 (3.0)	0.60
Unit on culture date[b]			
Emergency	14 (35.0)	94 (34.8)	0.60
Intensive care	4 (10.0)	43 (15.9)	
Other	22 (55.0)	133 (49.3)	

Table II. Healthcare exposures and culture characteristics among patients with mupirocin-resistant (cases) or mupirocin susceptible (controls) methicillin-resistant *Staphylococcus aureus* (cont).

Covariates	Cases N = 40	Controls N = 270	P-value
Colonization and/or infection[b]			
Colonization	23 (57.5)	145 (53.7)	0.48
Infection	9 (22.5)	84 (31.1)	
Colonization and infection	8 (20.0)	41 (15.2)	

Data are no. (%).

[a] Devices present during the inpatient admission before the culture date.

[b] Two degrees of freedom.

Table III. Antibiotic exposures in the previous year[a] among patients with mupirocin-resistant (cases) or mupirocin susceptible (controls) methicillin-resistant *Staphylococcus aureus*.

Antibiotics	Cases N = 40	Controls N = 270	P-value
Aminoglycoside	5 (12.5)	12 (4.4)	0.05
Beta-lactam	20 (50.0)	119 (44.1)	0.48
Cephalosporin, 1st generation	12 (30.0)	65 (24.1)	0.42
Cephalosporin, 2nd generation	4 (10.0)	18 (6.7)	0.50
Cephalosporin, 3rd generation	10 (25.0)	48 (17.8)	0.27
Cephalosporin, 4th generation (cefepime)	9 (22.5)	22 (8.2)	0.01
Fluoroquinolone	25 (62.5)	128 (47.4)	0.08
Lincosamide	2 (5.0)	21 (7.8)	0.75
Linezolid	2 (5.0)	8 (3.0)	0.62
Macrolide	7 (17.5)	81 (30.0)	0.10
Metronidazole	11 (27.5)	53 (19.6)	0.25
Mupirocin	7 (17.5)	10 (3.7)	<0.01
Sulfamethoxazole/trimethoprim	10 (25.0)	37 (13.7)	0.06
Vancomycin	18 (45.0)	70 (25.9)	0.01

Data are no. (%).

[a] Exposures in the year before the culture date, at least one dose.

Table IV. Predictors of mupirocin resistance in methicillin-resistant *Staphylococcus aureus*.

Covariates	Crude[1]		Adjusted[2]		
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	P-value
Mupirocin-resistant					
Cefepime[a]	3.08	1.28-7.41	2.80	1.03-7.58	0.04
Mupirocin[a]	5.02	1.75-14.44	9.84	2.93-33.09	<0.01
P. aeruginosa infection[b]	6.60	1.81-24.07	4.85	1.20-19.61	0.03
Low-level mupirocin-resistant					
Mupirocin[a]	3.88	1.08-13.92	6.32	1.58-25.33	<0.01
P. aeruginosa infection[b]	6.66	1.43-30.96	8.50	1.76-41.11	<0.01
High-level mupirocin-resistant					
Mupirocin[a]	6.45	1.33-31.27	11.18	1.89-66.30	<0.01

[1] Estimated from conditional logistic regression.

[2] Estimated from conditional logistic regression, adjusted by age, race, and predictors.

[a] Exposures in the year before the culture date, at least one dose.

[b] *Pseudomonas aeruginosa* infection in the year prior to admission.