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Predictors of community-associated *Staphylococcus aureus*, methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* skin and soft tissue infections in primary-care settings

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SUMMARY

Skin and soft tissue infections (SSTIs) due to *Staphylococcus aureus* have become increasingly common in the outpatient setting; however, risk factors for differentiating methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) SSTIs are needed to better inform antibiotic treatment decisions. We performed a case-case-control study within 14 primary-care clinics in South Texas from 2007 to 2015. Overall, 325 patients [*S. aureus* SSTI cases (case group 1, $n = 175$); MRSA SSTI cases (case group 2, $n = 115$); MSSA SSTI cases (case group 3, $n = 60$); uninfected control group (control, $n = 150$)] were evaluated. Each case group was compared to the control group, and then qualitatively contrasted to identify unique risk factors associated with *S. aureus,* MRSA, and MSSA SSTIs. Overall, prior SSTIs [adjusted odds ratio (aOR) 7·60, 95% confidence interval (CI) 3·31–17·45], male gender (aOR 1·74, 95% CI 1·06–2·85), and absence of healthcare occupation status (aOR 0·14, 95% CI 0·03–0·68) were independently associated with *S. aureus* SSTIs. The only unique risk factor for community-associated (CA)-MRSA SSTIs was a high body weight (⩾110 kg) (aOR 2·03, 95% CI 1·01–4·09).

Key words: Epidemiology, soft tissue infections, *Staphylococcus aureus*.

INTRODUCTION

The incidence of outpatient and emergency-department visits for skin and soft tissue infections (SSTIs) has substantially increased with the emergence of community-associated methicillin-resistant *S. aureus* (CA-MRSA) [1]. In the United States, about 80–90% of SSTIs are due to *S. aureus* [2]. Moreover, there is significant geographical diversity in the prevalence of CA-MRSA and methicillin-susceptible *S. aureus* (MSSA) strains in the community setting. Understanding the risk factors for CA-MRSA can help direct public health interventions and guide clinical management; however, the ability of traditional and newly identified

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risk factors to distinguish CA-MRSA infections from CA-MSSA infections has been widely inconsistent and population dependent. Several studies have investigated risk factors for CA-MRSA SSTIs, but these have been primarily based among inpatients or post-hospitalized patients, paediatric populations, and in the context of outbreak investigations [3–6]. Studies focusing on the adult community population are limited [7] and prior studies have been compromised by a lack of an uninfected control group. Such a comparison is important in identifying distinct risk factors for the development of community-associated *S. aureus* SSTIs and to distinguish unique risk factors for MRSA from MSSA.

We have recently described the prevalence and treatment characteristics of CA-MRSA SSTIs in South Texas in the primary-care setting [8, 9]. The objective of this study was to investigate risk factors for CA-MRSA SSTI and CA-MSSA SSTI compared to uninfected controls.

METHODS

We performed this investigation among a well-described cohort of patients with SSTIs in the primary-care setting; details of this cohort have been described previously [8, 9]. The study was conducted in collaboration with 14 clinics within the South Texas Ambulatory Research Network (STARNet), a practice-based research network composed of 108 urban, suburban, and rural primary-care clinics distributed throughout the South Texas region, from 2007 to 2015. Patients were eligible for study enrolment if they provided informed consent, were aged $\geqslant$18 years, and presented to one of the participating clinics with a SSTI. Control patients were enrolled through a subsequent prospective study within the same participating clinics and were eligible for study enrolment if they met the consent and age criteria above but did not have a SSTI or other infection from January 2015 to May 2015. Healthcare providers collected patient information.

A nested case-case-control study was conducted to identify risk factors associated with MRSA and MSSA SSTIs compared to controls [10]. Four study groups were defined: case group 1 comprised patients with either MRSA or MSSA SSTIs to represent CA-*S. aureus* as one risk group ($n = 175$). Case group 2 comprised patients with MRSA SSTIs ($n = 115$). Case group 3 comprised patients with MSSA SSTIs ($n = 60$). The uninfected control group (control) comprised patients who presented to these clinics without an SSTI, and represented the 'at risk' community population ($n = 150$). This method allowed us to assess the effect difference of infections due to methicillin-susceptible strains, those with methicillin-resistant strains, and those shared by both, compared to the same controls.

For microbiological analyses, samples were plated onto blood agar plates (TSA with 5% sheep blood; Fisher Scientific, USA) and incubated at 35–37 °C for 24 h, then subcultured to MRSA selective agar (MRSA*Select* chromogenic agar plates; Bio-Rad Laboratories, USA). Latex agglutination tests (StaphAurex®; ThermoFisher Scientific, USA), and phenotypic screening tests (cefoxitin resistance using VITEK 2 AST-GP75 cards, bioMérieux, USA) were used for the isolation and identification of MRSA. Antimicrobial minimum inhibitory concentrations were interpreted according to the Clinical and Laboratory Standards Institute document M100-S24 (2014) [11].

Clinical information collected included patient gender, race (Black, White, Other), ethnicity (Hispanic, Non-Hispanic), past medical history (e.g. diabetes, peripheral vascular disease, chronic non-infectious skin disorder, HIV/AIDS, cancer, actively receiving chemotherapy, immunosuppression), healthcare-related work history, skin infection history, height, weight, infection characteristics (e.g. location, duration, size, deepest tunnel depth, erythema, smell, ulceration, drainage, abscess, satellites), incision and drainage procedures received, and antibiotics prescribed. A weight $\geqslant$110 kg was used to indicate 'high body weight'. This is consistent with previous literature associating high body weight with antimicrobial dosing outcomes [12, 13].

Bivariable analyses were conducted comparing patient demographics, comorbidities, and exposures of each case group to the control group. Categorical variables were evaluated using Pearson's χ^2 or Fisher's exact test, and continuous variables were evaluated with Student's t test or Wilcoxon rank sum test. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported. For multivariable analyses, three backward stepwise logistic regression models were conducted for each case group reporting adjusted ORs (aORs) and 95% CIs. Variables were entered into the models if: (1) their P values were <0·10 in the bivariable between-group analyses; and (2) more than 5% of the study cohort had the presence of the variables. $P \leqslant 0{\cdot}05$ was used to determine statistical

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significance. Finally, we qualitatively considered the independent predictors for each comparison to identify only those uniquely associated with MRSA or MSSA SSTIs. SPSS v. 22.0 (IBM Corp, USA) was used for all statistical comparisons.

RESULTS

Overall, 175 patients with *S. aureus* SSTIs were evaluated: 115 patients with MRSA-positive cultures and 60 patients with MSSA-positive cultures. One hundred and fifty patients with no SSTI were enrolled as controls. Table 1 depicts the bivariable analyses and Table 2 depicts the multivariable analyses.

Case-control study 1: *S. aureus* SSTI cases *vs.* controls

In bivariable analysis, patients with *S. aureus* SSTIs were more likely to report a prior SSTI in the last 90 days (OR 5·84, 95% CI 2·75–12·40), more likely to weigh ⩾110 kg (OR 1·92, 95% CI 1·06–3·46), more likely to be male (OR 1·70, 95% CI 1·09–2·65), and less likely to have a healthcare occupation (OR 0·11, 95% CI 0·30–0·51) compared to controls. In multivariable analysis, prior SSTIs (aOR 7·60, 95% CI 3·31–17·45), male gender (aOR 1·74, 95% CI 1·06–2·85), and absence of healthcare occupation status (aOR 0·14, 95% CI 0·03–0·68) were independently associated with *S. aureus* SSTIs. A high body weight was not statistically significant (aOR 1·58, 95% CI 0·82–3·06).

Case-control study 2: MRSA SSTI cases *vs.* controls

In bivariable analysis, most patient demographics including age, male gender, race, and ethnicity were similar between MRSA SSTI cases and controls. Furthermore, there was no difference in the frequency of prior antimicrobial exposures between the two groups. Patients with MRSA SSTIs were more likely to report a prior SSTI in the last 90 days (OR 7·53, 95% CI 3·54–16·42), more likely to weigh ⩾110 kg (OR 2·54, 95% CI 1·34–4·81), and less likely to have a healthcare occupation (OR 0·16, 95% CI 0·04–0·71) compared to controls. In multivariable analysis, a history of prior SSTI in the last 90 days (aOR 7·98, 95% CI 3·37–18·88), high body weight (⩾110 kg) (aOR 2·03, 95% CI 1·01–4·09), and healthcare occupation (aOR 0·15, 95% CI 0·03–0·74) were independently associated with MRSA SSTIs.

Case-control study 3: MSSA SSTI cases *vs.* controls

In bivariable analyses, patients with MSSA SSTIs were significantly more likely to report a prior SSTI (OR 3·12, 95% CI 1·22–8·33), more likely to be male (OR 2·57, 95% CI 1·39–4·84), and less likely to have a healthcare occupation (OR 0·90, 95% CI 0·85–0·95) compared to controls. In multivariable analysis, a history of prior SSTI in the last 90 days (aOR 4·82, 95% CI 1·75–13·29), male gender (aOR 2·01, 95% CI 1·03 to 3·94), and healthcare occupation (aOR 0·17, 95% CI 0·02–0·88) were independently associated with MSSA SSTIs.

Qualitative comparison of models

Male gender, non-healthcare occupation, and prior SSTIs were predictors for *S. aureus* as an overall entity. After qualitative comparison of risk factors for MRSA SSTIs and MSSA SSTIs compared to controls, a high body weight (⩾110 kg) was a unique risk factor for MRSA SSTI cases, while male gender was the only unique risk factor for MSSA cases.

DISCUSSION

Over the past 10 years, ambulatory care visits for SSTIs have increased [14]. The worldwide emergence of CA-MRSA strains has made the management of *S. aureus* SSTIs extremely complicated and challenging. A clinical approach to the management of *S. aureus* SSTIs is to identify risk factors that can predict and possibly differentiate infections with MRSA and MSSA.

In this study, we found that a high body weight (⩾110 kg) was associated with CA-MRSA-related SSTIs. Obesity has been a known risk factor for SSTIs; however, the association between obesity or high body weight and CA-MRSA-related SSTIs has not been widely recognized. An outbreak investigation among New York football players identified a higher BMI and sharing towels were independently associated with MRSA infections [5]. More recently, Khawcharoenporn *et al.* identified obesity to be an independent risk factor for MRSA SSTIs compared to patients with SSTIs due to other bacterial aetiologies [15]. One hypothesis is that the higher risk MRSA SSTIs in this population may represent a manifestation of virulence factors such as the arginine catabolic mobile element (ACME) associated with USA300 CA-MRSA strains. Specifically, the *speG* gene within

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Table 1. *Bivariable analyses of risk factors associated with community-associated methicillin-resistant* S. aureus*, methicillin-susceptible* S. aureus*, and* S. aureus *skin and soft tissue infections compared to non-infected controls*

Characteristic	MRSA ($n = 115$)	MSSA ($n = 60$)	*S. aureus* ($n = 175$)	Controls ($n = 150$)	MRSA *vs.* controls *P*	MSSA *vs.* controls *P*	*S. aureus vs.* controls *P*
Mean age, years (±S.D.)	40 (±13)	42 (±14)	41 (±13)	43 (±14)	0·27	0·70	0·30
Male	53 (46%)	36 (60%)	89 (51%)	58 (39%)	0·21	<0·01*	0·02*
Race/ethnicity							
Black	8 (7%)	1 (2%)	9 (5%)	12 (8%)	0·77	0·12†	0·37
Hispanic	86 (75%)	47 (78%)	133 (76%)	119 (79%)	0·45	0·78	0·59
Diabetes	25 (22%)	17 (28%)	44 (25%)	34 (23%)	0·89	0·17	0·60
Weight ≥110 kg	29 (25%)	11 (18%)	37 (21%)	20 (13%)	<0·01*	0·82	0·04*
Chronic non-infectious skin disorder	0	1 (2%)	1 (1%)	3 (2%)	1·00†	0·39†	1·00†
HIV	0	0	0	1 (1%)	1·00†	1·00†	1·00†
Cancer	0	0	0	5 (3%)	0·58†	1·00†	0·33†
Provides healthcare to others	2 (2%)	1 (2%)	3 (2%)	15 (10%)	<0·01*†	<0·01*†	<0·01*†
Prior SSTI	37 (32%)	10 (17%)	47 (27%)	9 (6%)	<0·01*	0·01*	<0·01*
Prior antibiotics within 90 days	18 (16%)	9 (15%)	27 (15%)	26 (17%)	0·74	0·72	0·76

MRSA, Methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; S.D., standard deviation; HIV, human immunodeficiency virus; SSTI, skin and soft tissue infection.

No patients had history of peripheral vascular disease or chemotherapy.

* Statistically significant.

† Fisher's exact test was used.

Table 2. *Multivariable analyses of risk factors for community-associated* S. aureus*, methicillin-resistant* S. aureus*, and methicillin-susceptible* S. aureus *skin and soft tissue infections compared to non-infected controls*

	S. aureus vs. controls		MRSA *vs.* controls		MSSA *vs.* controls	
Variables	aOR (95% CI)	*P*	aOR (95% CI)	*P*	aOR (95% CI)	*P*
Male	1·74 (1·06–2·85)	0·04			2·01 (1·03–3·94)	0·04
Healthcare provider	0·14 (0·03–0·68)	<0·01	0·15 (0·03–0·74)	0·02	0·17 (0·02–0·88)	0·02
Weight ≥110 kg	1·58 (0·82–3·06)	0·17	2·03 (1·01–4·09)	0·04		
History of prior SSTI	7·60 (3·31–17·45)	<0·01	7·98 (3·37–18·88)	<0·01	4·82 (1·75–13·29)	<0·01

MRSA, Methicillin resistant *S. aureus*; MSSA, methicillin susceptible *S. aureus*; SSTI, skin and soft tissue infection; aOR, adjusted odds ratio; CI, confidence interval.

the ACME locus was found to be associated with increased resistance to polyamines that are produced on the skin, which are toxic to other *S. aureus* strains [16, 17]. This fitness advantage of ACME-containing MRSA strains, coupled with the changes that compromise skin structure in patients with high body fat, may cause a specific pathogen–host interaction in this population [18, 19]. This increased risk for MRSA SSTIs, and not MSSA SSTIs, in patients with high body weight merits further investigation, particularly because obese patients have been associated with increased risk for complications and recurrences of infection [19].

Male gender was a distinct independent risk factor for MSSA SSTIs. This finding contrasts with other studies that showed no significant gender predominance nor identified male gender to be a risk factor for MRSA infections [20, 21]. The majority of studies describing the relationship of men and MRSA infections were conducted in institutionalized settings, men who have sex with men populations, sports teams, and military recruits. Conversely, studies have shown that men are at higher risk for MSSA bacteraemia and MSSA colonization [22–24]. Colonization has been shown to be an important risk factor preceding infections; this may, in part, reflect a higher incidence of MSSA SSTIs in men. However, we did not account for colonization in this study. Other possible reasons why gender may play a role in developing MSSA or MRSA infections include different health-seeking behaviours, social behaviours (e.g. occupation, recreational activities), the infecting clones, or hormonal differences. Regardless, these are mostly speculative and further epidemiological investigation is needed.

There are limitations to this study. First, we did not account for social and behavioural risk factors that may be associated with *S. aureus* SSTIs and/or clinical outcomes. Second, we used laboratory diagnosis to identify *S. aureus* cases. Patients presenting with SSTIs with no culture or with culture-negative results may have different characteristics. SSTIs can be caused by a variety of pathogens, including *S. aureus*, streptococci, and Gram-negative bacteria. This study focused on the subset of patients with positive cultures for *S. aureus*. These patients may present differently from the general SSTI population. Further, based on the inclusion criteria, patients without suspected MRSA infections may not have been accounted for. The small sample size limited the ability to identify risks associated with lower exposures. Another limitation is the long time period of the study, during which secular trends of CA-MRSA have been described [25, 26]. Finally, there may be limited generalizability to other regions outside of South Texas. Strengths of this study include the case-case-control design to assess potential epidemiological risk factors for community-associated *S. aureus* infections compared to uninfected controls and to distinguish between MRSA and MSSA. This methodology allowed us to identify common and unique risk factors that were associated with MRSA or MSSA SSTIs. Finally, this study was based in the primary-care setting, adding important findings to the sparse literature in this growing population.

In summary, in outpatients with *S. aureus* SSTIs in South Texas, we found minimal differences in predictors for MRSA and MSSA SSTIs. Overall, prior SSTIs, male gender, and non-healthcare occupation were predictors for *S. aureus* SSTIs. The only unique risk factor for CA-MRSA SSTIs was a high body weight.

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DECLARATION OF INTEREST

None.

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