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Comparing the epidemiology of hospital-acquired methicillin-resistant *Staphylococcus aureus* clone groups in Alberta, Canada

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SUMMARY

Patients with methicillin-resistant *Staphylococcus aureus* (MRSA) clones, which were traditionally seen in the community setting (USA400/CMRSA7 and USA300/CMRSA10), are often identified as hospital-acquired (HA) infections using Infection Prevention and Control (IPC) surveillance definitions. This study examined the demographics and healthcare risk factors of patients with HA-MRSA to help understand if community MRSA clones are from a source internal or external to the hospital setting. Despite USA300/CMRSA10 being the predominant clone in Alberta, hospital clones (USA100/CMRSA2) still dominated in the acute care setting. In the Alberta hospitalized population, patients with USA400/CMRSA7 and USA300/CMRSA10 clones were significantly younger, had fewer comorbidities, and a greater proportion had none or ambulatory care-only healthcare exposure. These findings suggest that there are two distinct populations of HA-MRSA patients, and the patients with USA400/CMRSA7 and USA300/CMRSA10 clones identified in hospital more greatly resemble patients affected by those clones in the community. It is possible that epidemiological assessment overidentifies HA acquisition of MRSA in patients unscreened for MRSA on admission to acute care.

Key words: Infectious disease control, infectious disease epidemiology, molecular epidemiology, MRSA, surveillance.

INTRODUCTION

Staphylococcus aureus is one of the most common causes of hospital-acquired (HA) infections [1]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major burden on the healthcare system and is associated with greater morbidity and mortality compared to methicillin-susceptible *S. aureus* [1]. In Canadian hospitals, the 2009 incident MRSA infection rate was 3·8/10 000 patient-days [2]. MRSA is also reported in the general community, where population MRSA infection rates were 10·7/10 000 population in 2009 [3, 4].

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Over time, distinct MRSA clones have emerged in the community setting as well as in the acute care setting [5, 6]. In Canada, there are ten recognized epidemic clones of MRSA based on pulsed-field gel electrophoresis (PFGE) patterns (CMRSA1–10), with USA400/CMRSA7 and USA300/CMRSA10 having arisen in the community and USA100/CMRSA2 seen first in the acute care setting [7]. USA300/CMRSA10 has become a predominant strain of MRSA, causing the majority of skin and soft tissue infections in the community [8]. In recent years, increased infections from USA400/CMRSA7 and USA300/CMRSA10 clones have been associated with HA-MRSA infections [9–11]. Canadian hospitals estimate these clones account for about 25% of all HA-MRSA infections [10]. Compared to infections from USA100/CMRSA2 clones, USA400/CMRSA7 and USA300/CMRSA10 clones are currently a concern for acute care facilities because they may have greater survival fitness, capacity for transmission, and poorer patient outcomes [11, 12].

It is unclear if HA-MRSA patients with USA400/CMRSA7 and USA300/CMRSA10 clones acquire those during their acute care encounter or if they are already colonized prior to their hospital visit [5]. This study compares the demographics and healthcare risk factors of HA-MRSA patients and their molecular clone types to help understand if USA400/CMRSA7 and USA300/CMRSA10 clones are from a source internal or external to the hospital setting. The purpose of this study is to indicate if patients with USA400/CMRSA7 and USA300/CMRSA10 clones are overidentified as HA when using current epidemiological surveillance definitions.

METHODS

Study population

The province of Alberta, Canada spans 661 190 km^2 with a population of ~4 million residents with all healthcare delivery provided by Alberta Health Services and its contracted partner Covenant Health (AHS/COV) [13]. In the 2012/2013 fiscal year, AHS/COV provided 3 014 422 hospital patient-days across 101 acute care facilities in five geographical zones. Patients in all acute care hospitals undergo MRSA admission screening if there is a prior history of hospitalization or institutionalization of 24–48 h or more in the past 6 months [14]. In addition, the zones may perform additional screening based on local MRSA epidemiology or for specific patient populations (e.g. patients undergoing cardiovascular procedures).

Collecting and classifying MRSA

The provincial Infection Prevention and Control (IPC) programme monitors incident MRSA cases from all acute care sites in the province in a complete surveillance network [9, 15]. Infection control professionals (ICPs) classify cases as HA where a patient is newly identified as MRSA positive >48 h after admission, and determine infections using the definitions from the National Healthcare Safety Network (NHSN) [9, 16]. The Alberta Provincial Laboratory for Public Health (ProvLab) performs *Staphylococcus* protein A (*spa*) typing and PFGE typing as described by Mulvey *et al.* annually on a patient's first clinical MRSA isolate as described previously [9, 17]. PFGE profiles are grouped into CMRSA epidemic clones according to the Canadian MRSA classification system [7].

Cases classified as HA-MRSA were matched to ProvLab data over the 2-year period as described previously [9]. Since ProvLab types only one MRSA clinical isolate per patient in a year from any community or acute care setting, additional ProvLab data (i.e. from January 2010 to March 2013) were included. Administrative datasets (Discharge Abstract Database; Admission Discharge Transfer; National Ambulatory Care Reporting System; Alberta Continuing Care Information System) were matched to the study population using provincial healthcare number, last name, and date of birth for the 12 months before the HA-MRSA culture date to identify healthcare exposures. Data elements included patient's demographics (gender, date of birth), previous healthcare exposure (acute care admissions, ambulatory care visits, long-term care residents), and International Statistical Classification of Diseases and Related Health Problems – 10th Revision, Canada (ICD-10-CA) diagnostic codes [18].

Data analysis

USA400/CMRSA7 and USA300/CMRSA10 clones were compared to USA100/CMRSA2 over the 2-year period. Several factors were analysed, such as cultured anatomical site, time to detection of positive MRSA culture, previous healthcare encounters, and Charlson comorbidities using the StataCorp StataIC package software v. 10 [19, 20]. Univariate comparisons of proportions were performed for categorical variables and the Mann–Whitney U test for continuous,

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non-normally distributed variables. For all statistical comparisons $P < 0{\cdot}05$ was deemed statistically significant.

A binary logistic regression model was used to study the association between a patient's demographic information and healthcare history, with the detection of traditionally community (*vs.* traditionally hospital) clones. The model included: gender (male *vs.* female), age (years), time to a positive test (days), previous healthcare exposure (no exposure, long-term care, or ambulatory-only *vs.* previously an inpatient), total count of healthcare visits, the specimen site MRSA infections were isolated from (sterile fluids, skin and soft tissue, respiratory *vs.* urine), and the number of pre-existing comorbid conditions. The multivariable model was selected by stepwise backward elimination using a cut-off of $\alpha = 0{\cdot}25$ to prevent any clinically relevant variables from being excluded.

Once selected, full combinatorial interaction terms were entered simultaneously to see if they added any significant information to the model. The Hosmer–Lemeshow χ^2 test determined model fit for both main effects and interactions. The presence of multi-collinearity was assessed by linear regression of each independent variable on all the others, and the variance inflation factor. Those variables with a variance inflation factor >10 likely contained multi-collinearity and were candidates for removal. All tests of significance on the final model were performed at the 5% level using IBM SPSS v. 19 (IBM Corp., USA).

Ethics statement

IPC conducts mandatory surveillance to monitor healthcare-associated infections in all acute care facilities in the province. A Project Ethics Community Consensus Initiative was completed. Based upon six ethical considerations, the project was deemed to be under the IPC mandate for quality improvement and approved to meet ethical standards; written consent was not required for this analysis. The project data were collected in the provincial IPC surveillance database in patient-identified form; however, for analysis all data were de-identified and project results are presented in aggregate format. Existing privacy impact agreements between ProvLab and Alberta Health Services enabled analysis of patient-level data.

RESULTS

The provincial rate of HA-MRSA infections was 0·77/10 000 patient-days between April 2011 and March 2013, and there were 770 HA-MRSA cases identified from the IPC-ProvLab data linkage. About 90% of these fell into two major clone groups: USA100/CMRSA2 (501/770, 65·1%) or USA400/CMRSA7 ($n = 47$) and USA300/CMRSA10 ($n = 160$) (combined 207/770, 26·8%) (Table 1). The remaining 62 cases (8·1%) were a heterogeneous mix of five PFGE types and 25 unique *spa* types (see Supplementary Table S1).

Binary logistic regression retained good fit to the data (Hosmer and Lemeshow $\chi^2 = 5{\cdot}80$, D.F. = 8, $0{\cdot}60 < P < 0{\cdot}70$) and revealed that, compared to USA100/CMRSA2, USA400/CMRSA7 and USA300/CMRSA10 cases were significantly younger, and more likely to be cultured from a sterile fluid, skin and soft tissue, or respiratory infection (Table 2). No significant difference in the number of comorbid conditions was found in the model; however, the univariate analysis found that individuals with USA100/CMRSA2 clones had significantly higher frequencies of comorbid conditions such as congestive heart failure, peripheral vascular disease, dementia, and renal disease (Table 1).

Patients with ambulatory-only visits who presented $\geqslant 5$ times to ambulatory care in the previous 12 months represented 10·6% (82/770) of all HA-MRSA clones (Fig. 1). USA400/CMRSA7 and USA300/CMRSA10 cases had either no previous history of being admitted to an Alberta hospital, or were exposed (only) through ambulatory visits to an emergency department prior to the study period (Table 2). Including interaction terms did not add significant information to the model ($\chi^2 = 12{\cdot}02$, D.F. = 13, $0{\cdot}50 < P < 0{\cdot}60$). No significant multi-collinearity was detected in the final main-effects model.

DISCUSSION

This study shows that in an extensive, collaborative province-wide surveillance network two distinct MRSA clone groups predominate in HA-MRSA patients, with the common *spa* types observed for these MRSA clones already reported [9]. The USA100/CMRSA2 clone resembles HA-MRSA seen in other studies, consisting of an older population with more urinary infections reported [10, 12]. The distribution of USA400/CMRSA7 and USA300/CMRSA10 within the HA-MRSA population resembles that of community-acquired (CA) MRSA in the province [4, 21]. MRSA clones traditionally considered as community type resemble those described for community-identified MRSA; predominately affecting

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Table 1. *Epidemiological characteristics of patients with hospital-acquired methicillin-resistant* Staphylococcus aureus *(HA-MRSA) from USA100/CMRSA2 or USA400/CMRSA7 and USA300/CMRSA10 clones in Alberta, Canada (April 2011–March 2013)*

Variable	USA100/CMRSA2 ($N = 501$), *n* (%)	USA400/CMRSA7 and USA300/CMRSA10 ($N = 207$), *n* (%)	*P* value*
Age (years)			
Median [IQR]	76·4 [24·1]	56·4 [33·7]	<0·05
Gender			
Male	244 (48·7)	115 (55·6)	0·10
Time to detection (days)			
Median [IQR]	22·0 [35·0]	14·0 [29·0]	<0·05
Previous healthcare exposure			
None	60 (12·0)	37 (17·9)	<0·05
Long-term care resident	16 (3·2)	3 (1·4)	0·19
Ambulatory care only	146 (29·1)	81 (39·2)	<0·05
Inpatient ± ambulatory	279 (55·6)	86 (41·5)	<0·05
Specimen types			
Clinical culture site	$n = 369$ (73·7)	$n = 163$ (78·7)	0·15
Blood	21 (5·7)	13 (8·0)	0·32
Other sterile	34 (9·2)	16 (9·8)	0·83
Skin and soft tissue	162 (43·9)	88 (54·0)	<0·05
Infected device	13 (3·5)	7 (4·3)	0·67
Respiratory	50 (13·6)	30 (18·4)	0·15
Urine	89 (24·1)	9 (5·5)	<0·05
Comorbidity information available			
Yes	439 (87·6)	169 (81·6)	
No	62 (12·4)	38 (18·4)	
Charlson comorbidities	($n = 439$)	($n = 169$)	
Myocardial infarction	29 (6·6)	5 (3·0)	0·08
Congestive heart failure	55 (13·5)	11 (6·5)	<0·05
Peripheral vascular disease	29 (6·6)	2 (1·2)	<0·05
Cerebrovascular disease	20 (4·6)	5 (3·0)	0·37
Dementia	38 (8·7)	5 (3·0)	<0·05
Chronic pulmonary disease	71 (16·2)	22 (13·0)	0·33
Rheumatic disease	9 (2·1)	4 (2·4)	0·81
Peptic ulcer disease	7 (1·6)	1 (0·6)	0·33
Mild liver disease	14 (3·2)	3 (1·8)	0·34
Uncomplicated diabetes	89 (20·3)	29 (17·2)	0·38
Complicated diabetes	81 (18·5)	21 (12·4)	0·07
Hemiplegia or paraplegia	13 (3·0)	4 (2·4)	0·69
Renal disease	37 (8·4)	6 (3·6)	<0·05
Any malignancy	46 (10·5)	19 (11·2)	0·79
Moderate/severe liver disease	5 (1·1)	2 (1·2)	0·96
Metastasis solid tumour	29 (6·6)	7 (4·1)	0·25
AIDS/HIV infection	0	0	n.a.
Frequency of comorbidities			
0	179 (40·8)	91 (53·8)	<0·05
1	108 (24·6)	42 (24·9)	0·95
2	60 (13·7)	20 (11·8)	0·55
$\geqslant 3$	92 (21·0)	16 (9·5)	<0·05

* *P* values from *z* test to compare proportions or Mann–Whitney *U* test to compare medians; n.a., not applicable.
Sixty-two MRSA isolates not included in this study of total population ($n = 770$). These isolates represented five PFGE types and 30 unique *spa* types.

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Table 2. *Adjusted odds ratios obtained by a backward-selected, multivariable, logistic regression model of the association between the three listed variables and the detection of USA400/CMRSA7 and USA300/CMRSA10 clones (N = 207), compared to USA100/CMRSA2 (N = 501)*

Variables	OR (95% CI)	*P* value
Age (years)	0·97 (0·96–0·98)	<0·05
Previous healthcare exposure		
No exposure (*vs.* previous inpatient)	1·61 (0·83–3·11)	0·16
Long-term care (*vs.* previous inpatient)	1·01 (0·21–5·68)	0·91
Ambulatory only (*vs.* previous inpatient)	1·65 (1·03–2·62)	<0·05
Site of infection		
Sterile fluids (*vs.* UTI)	3·56 (1·52–8·34)	<0·05
Skin and soft tissue (*vs.* UTI)	3·95 (1·85–8·44)	<0·05
Respiratory (*vs.* UTI)	3·36 (1·37–8·28)	<0·05

OR, Odds ratio; CI, confidence interval; UTI, urinary tract infection.

younger populations with fewer comorbidities and more likely to present with skin and soft tissue infections [10, 12]. A significant difference was seen between CA and HA in a previous review of all MRSA bloodstream infection (BSI); however, this finding was not seen in this study since only the first BSI episode and not recurrent episodes were captured [15].

In our study, patients with USA400/CMRSA7 and USA300/CMRSA10 clones had a shorter time to positive culture compared to those with USA100/CMRSA2. A shorter time to detection would suggest that patients were colonized with MRSA on admission, and later misclassified as HA-MRSA. Similarly, a study by Popovich *et al.* [5] found that in patients with hospital-onset BSI, there was a trend towards a shorter time to positive culture associated with community MRSA clones, suggesting that nosocomial infections were due to endogenous community MRSA.

Limited resources for admission screening and the necessity for provincially standardized surveillance definitions may result in overidentification of patients with HA-MRSA. To ensure that transmission events are detected accurately in the healthcare setting, surveillance definition time-frames should be amended to increase the specificity of cases identified in the HA category.

USA100/CMRSA2 cases are older and more likely to have comorbid conditions than those with USA400/CMRSA7 and USA300/CMRSA10 clones, as would be expected due to their increased age [12]. Individuals with exposure to healthcare are more likely to be identified with a USA100/CMRSA2 clone, since inpatient admission is a known risk factor [11]. In this study, a larger proportion of patients with the USA400/CMRSA7 and USA300/CMRSA10 clones had ambulatory-only exposure in the year before MRSA identification. This corresponds to the results of a study done by Nichol *et al.* [12], where patients swabbed at different locations in a hospital identified USA400/CMRSA7 and USA300/CMRSA10 clones predominantly in the emergency department. In Alberta data, nearly 11% of patients with any HA-MRSA clone had $\geqslant 5$ ambulatory care visits in the previous 12 months (Fig. 1), suggesting that frequent visits to ambulatory care may be worth considering as a new risk factor for MRSA admission screening. This may identify additional patients with MRSA at time of admission and reduce potential healthcare MRSA transmission.

Simor *et al.* [10] suggested that individuals acquire USA400/CMRSA7 and USA300/CMRSA10 clones within the community and then introduce them to the healthcare setting. Of ongoing concern is that the continual exogenous introduction of the organism into acute care by the community reservoir over time could create endemnicity of these clones, which may have a higher capacity for transmission [11, 12]. Eventually there will be an inability to distinguish the USA400/CMRSA7 and USA300/CMRSA10 clones through patient demographic characteristics as they become equally distributed throughout the acute care patient population [10]. Therefore, a full epidemiological definition for MRSA in the healthcare setting should include information on molecular typing, IPC definitions assigning attribution of organism as healthcare or community based on time to detection from admission time, and describe infection onset as community or hospital [22].

This study has unique strengths, such as a single comprehensive surveillance network in a large Canadian jurisdiction and molecular typing for all isolates performed in a single reference laboratory. While other surveillance systems rely on individual hospitals or regions to submit surveillance data and to perform data quality reviews [23–25], the AHS/COV IPC surveillance system uses a web-based data-entry system where patient-level data are submitted to a single surveillance team, which performs province-wide education, data quality checks, and system performance evaluations.

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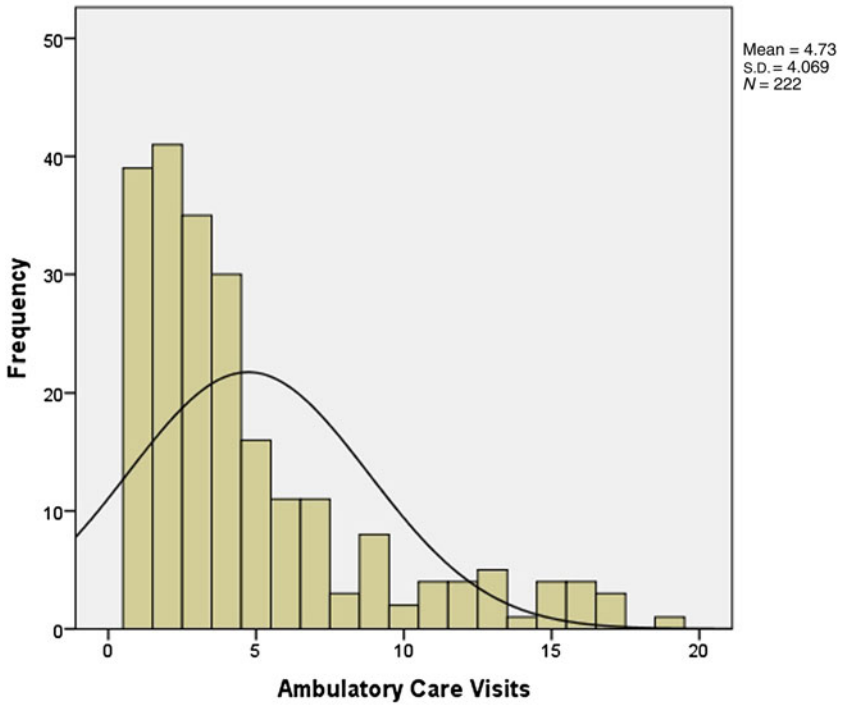

Fig. 1. Frequency distribution of ambulatory care visits. S.D., Standard deviation.

This study has limitations. First, there are limitations related to the local implementation of provincial screening guidelines. While admission screening for MRSA follows provincial guidelines [14], facilities may devise screening strategies based on local MRSA epidemiology so that patients may not have an equal chance of detection on admission to an acute care facility. The basis of IPC case classifications is on definitions, which rely on defined time-frames [16]. Already-colonized patients may be identified as HA-MRSA during their admission or may remain undetected and misclassified as CA-MRSA at some time >12 months after their first healthcare encounter. Second, only the first clinical isolate per year is submitted by a regional laboratory for typing at ProvLab. Therefore, a patient could acquire another MRSA clone within the year, which would not be identified. Additionally, ProvLab does not type screening isolates so typing data were not available for incident IPC cases from screening specimens, and this study cannot rule out the possibility of a patient having colonization and infection with different MRSA strains.

In conclusion, data from an extensive, collaborative surveillance network indicate that HA-MRSA occur in distinct populations. To date, the USA100/CMRSA2 clones remain predominant in the Alberta inpatient population and are epidemiologically distinct from USA400/CMRSA7 and USA300/CMRSA10 clones in the acute care setting. Patients with USA400/CMRSA7 and USA300/CMRSA10 clones more closely resemble patients with these clones identified in the community. Shorter times to detection and a higher frequency of ambulatory (only) visits may suggest that community MRSA clones are largely derived from an endogenous source [5, 12]. Considering frequent ambulatory care as a risk factor for MRSA colonization could be included in admission screening policies and may result in improved specificity in the current IPC surveillance definition. Ideally, this information will better protect patients, staff, and visitors from exposure to community MRSA clones in hospital.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268816000376.

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DECLARATION OF INTEREST

None.

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