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# Antimicrobial Susceptibilities of Health Care-Associated and Community-Associated Strains of Methicillin-Resistant *Staphylococcus aureus* from Hospitalized Patients in Canada, 1995 to 2008▽

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**We determined the *in vitro* antimicrobial susceptibilities of 7,942 methicillin-resistant *Staphylococcus aureus* (MRSA) isolates obtained from patients hospitalized in 48 Canadian hospitals from 1995 to 2008. Regional variations in susceptibilities were identified. The dissemination of community-associated strains in Canada appears to have contributed to increased susceptibility of MRSA to several non-β-lactam antimicrobial agents in the past decade. Reduced susceptibility to glycopeptides was not identified.**

The incidence of infections caused by health care-associated and community-associated strains of methicillin-resistant *Staphylococcus aureus* (MRSA) continues to increase in most parts of the world (4, 6). Community-associated MRSA (CA-MRSA) strains were initially reported to be more susceptible to various classes of antimicrobial agents than health care-associated MRSA (HA-MRSA) strains (16). However, this may no longer be true, particularly as CA-MRSA strains are increasingly being introduced into hospital settings (13, 18). Although glycopeptides have long been considered the treatment of choice for serious MRSA infections, concern has arisen because of the emergence and spread of strains with reduced susceptibility to vancomycin (7, 10, 12). In this study, we determined the *in vitro* susceptibilities of HA- and CA-MRSA strains obtained in national surveillance conducted in Canadian hospitals to commonly used systemic and topical antimicrobial agents. We were specifically interested in monitoring trends over time and regional differences across the country and determining whether there were differences in resistance profiles of CA-MRSA compared to HA-MRSA in Canada.

Prospective surveillance for MRSA in hospitalized patients has been conducted by the Canadian Nosocomial Infection Surveillance Program (CNISP) since 1995 (20–22). The CNISP involves 48 sentinel hospitals across Canada, working in collaboration with the Centre for Communicable Diseases and Infection Control and the National Microbiology Laboratory, both of the Public Health Agency of Canada. Most (94%) of the hospitals are tertiary care teaching hospitals, representing almost all of the university-affiliated medical centers in the country. To maintain site-specific confidentiality, the hospitals were grouped into one of three geographic regions: western Canada (16 hospitals from the provinces of British Columbia, Alberta, Saskatchewan, and Manitoba), central Canada (24 hospitals from Ontario and Quebec), and eastern Canada (8 hospitals from New Brunswick, Nova Scotia, and Newfoundland and Labrador).

Surveillance for MRSA was laboratory based, as previously described, and only hospitalized patients newly identified as colonized or infected with MRSA were included (20, 21). The medical records were reviewed to extract clinical and demographic information. The presence of infection caused by MRSA was determined using standard surveillance definitions (8). As the surveillance was observational, did not involve any change in patient care, and was considered to be within the usual scope of hospital-based infection prevention and control programs, research ethics board approval was not required.

MRSA isolates obtained from 1995 to 2008 were included in this study and submitted to a central laboratory for further characterization; only one isolate (generally the first) from each patient was included. All isolates were confirmed as MRSA by detection of the *nuc* and *mec* genes by PCR (14). All isolates submitted in 1995 and 1996 and a geographically representative subset of those submitted in each subsequent year were selected for antimicrobial susceptibility testing.

Antimicrobial susceptibility testing was done by broth microdilution in accordance with Clinical and Laboratory Standards Institute guidelines (3). Detection of inducible clindamycin resistance was done by the disk approximation D-zone

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test or by broth microdilution with a combined erythromycin (4.0 μg/ml) and clindamycin (0.5 μg/ml) well (3). Multidrug-resistant organisms were defined as those resistant to three or more non-β-lactam classes of antimicrobial agents.

All isolates were typed by pulsed-field gel electrophoresis (PFGE) following SmaI digestion of genomic DNA and analyzed using BioNumerics software, version 5.1 (Applied Maths, Austin, TX) (15, 22). Clonal similarities were derived from the unweighted pair group method using arithmetic averages (UPGMA) and based on Dice coefficients. Band position tolerance and optimization were set at 1.5% and 2.0%, respectively. A similarity coefficient of ≥80% was used to determine clonality. CA-MRSA strains were defined as PFGE types CMRSA-7 and CMRSA-10, resembling genotypes USA400 (multilocus sequence type 1 [ST1], clonal complex 1 [CC1]) and USA300 (ST8, CC8), respectively (2). These strains all had the staphylococcal cassette chromosome *mec* (SCC*mec*) type IV, as determined by PCR using previously described primers and methods (17).

A total of 7,942 unique patient isolates were available for antimicrobial susceptibility testing; the results are summarized in Table 1. There were no isolates with reduced susceptibility to vancomycin, and there was no increase in the vancomycin $MIC_{90}$, or change in the distribution of vancomycin MICs over time (data not shown). Resistance to linezolid, daptomycin, tigecycline, and ceftobiprole was not detected. The proportion of isolates resistant to certain antimicrobial agents decreased over time. The rates of resistance to clindamycin, tetracycline, and trimethoprim-sulfamethoxazole decreased from 92%, 31%, and 55%, respectively, in the first 5 years of surveillance (1995 to 1999) to 66%, 8%, and 7%, respectively, in the last 4 years of surveillance (2005 to 2008) ($P < 0.001$ for each antimicrobial agent). Overall, 2,594 (33%) isolates were multidrug resistant, but the proportion of multidrug-resistant isolates decreased from 60% of those recovered from 1995 to 1999 to 13% recovered between 2005 and 2008 ($P < 0.001$). The rates of high-level resistance to mupirocin increased over time from 2% to 6% ($P < 0.001$).

There were regional differences in MRSA antimicrobial susceptibilities in Canada. Isolates recovered from patients hospitalized in western provinces were less likely to be resistant to clindamycin (66% in the west versus 89% in the rest of the country; $P < 0.001$) and to ciprofloxacin (84% versus 93%; $P < 0.001$). However, they were more likely to be resistant to tetracycline (31% versus 7%; $P < 0.001$), trimethoprim-sulfamethoxazole (31% versus 23%; $P < 0.001$), gentamicin (14% versus 7%; $P < 0.001$), and mupirocin (6% versus 3%; $P < 0.001$). Similar regional differences were also found if only the last year of the surveillance was considered (data not shown). There were no significant differences in the antimicrobial susceptibilities of isolates from MRSA-infected patients compared to isolates from patients with MRSA colonization without infection (data not shown).

There were 1,316 CA-MRSA isolates (CMRSA-10/USA300 or CMRSA-7/USA400) and 6,626 HA-MRSA isolates (other PFGE genotypes). Compared to HA-MRSA strains, CA-MRSA strains were more likely to be susceptible to erythromycin, clindamycin, tetracycline, trimethoprim-sulfamethoxazole, ciprofloxacin, gentamicin, rifampin, and fusidic acid but were more likely to have high-level resistance to mupirocin (Table 2). CA-MRSA isolates

TABLE 1. Antimicrobial susceptibilities of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates recovered from patients hospitalized in 48 Canadian hospitals, 1995 to 2008

| Antimicrobial agent(s) or characteristic | Antimicrobial susceptibility of MRSA isolates | | | | | | | | | | *P* value[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall (1995–2008) | | | 1995–1999 | | | 2000–2004 | | | 2005–2008 | |
| | No. tested | $MIC_{90}$ (μg/ml) | % resistant | No. tested | $MIC_{90}$ (μg/ml) | % resistant | No. tested | $MIC_{90}$ (μg/ml) | % resistant | No. tested | $MIC_{90}$ (μg/ml) | % resistant | |
| Erythromycin | 7,942 | >8.0 | 92 | 2,696 | >8.0 | 94 | 2,006 | >8.0 | 93 | 3,240 | >8.0 | 89 | |
| Clindamycin | 7,522 | >4.0 | 79 | 2,276 | >4.0 | 92 | 2,006 | >4.0 | 83 | 3,240 | >4.0 | 66 | <0.001 |
| Tetracycline | 7,871 | >16 | 18 | 2,616 | >16 | 31 | 2,006 | >16 | 14 | 3,207 | ≤2.0 | 8 | <0.001 |
| TMP-SMX[b] | 7,942 | >8.0 | 27 | 2,696 | >8.0 | 55 | 2,006 | >8.0 | 16 | 3,240 | ≤0.25 | 7 | <0.001 |
| Ciprofloxacin | 7,942 | >8.0 | 89 | 2,696 | >8.0 | 91 | 2,006 | >8.0 | 89 | 3,240 | >8.0 | 87 | |
| Gentamicin | 4,639 | 16 | 11 | 0 | | | 1,399 | >16 | 14 | 3,240 | 2.0 | 8 | <0.001 |
| Rifampin | 7,870 | ≤0.25 | 2 | 2,624 | ≤0.25 | 2 | 2,006 | ≤0.25 | 2 | 3,240 | ≤0.25 | 1 | |
| Vancomycin | 7,942 | 1.0 | 0 | 2,696 | 1.0 | 0 | 2,006 | 1.0 | 0 | 3,240 | 1.0 | 0 | |
| Fusidic acid[c] | 7,533 | 0.5 | 6 | 2,287 | 0.5 | 5 | 2,006 | 1.0 | 8 | 3,240 | 0.5 | 5 | |
| Mupirocin[d] | 7,870 | 16 | 5 | 2,624 | 16 | 2 | 2,006 | 32 | 7 | 3,240 | 16 | 6 | <0.001 |
| Tigecycline | 1,953 | 0.5 | 0 | 0 | | | 0 | | | 1,953 | 0.5 | 0 | |
| Linezolid | 5,105 | 2.0 | 0 | 0 | | | 1,865 | 2.0 | 0 | 3,240 | 2.0 | 0 | |
| Daptomycin | 1,953 | 0.5 | 0 | 0 | | | 0 | | | 1,953 | 0.5 | 0 | |
| Ceftobiprole | 1,953 | 1.0 | 0 | 0 | | | 0 | | | 1,953 | 1.0 | 0 | |
| Multidrug resistant | 2,594 | | 33 | 1,624 | | 60 | 553 | | 28 | 417 | | 13 | <0.001 |

[a] Trends in proportions (percentage resistant) over time determined by the Cochrane-Armitage trend test.
[b] TMP-SMX, trimethoprim-sulfamethoxazole.
[c] Resistance to fusidic acid defined as exhibiting an MIC of ≥2.0 μg/ml (9).
[d] Resistance (high level) to mupirocin defined as exhibiting an MIC of ≥512 μg/ml (23).

TABLE 2. Antimicrobial susceptibilities of health care-associated MRSA and community-associated MRSA (CMRSA7/USA400 and CMRSA-10/USA300) isolates recovered from hospitalized patients in 48 Canadian hospitals, 1995 to 2008

| Antimicrobial agent(s) or characteristic | Antimicrobial susceptibility of MRSA isolates | | | | | |
|---|---|---|---|---|---|---|
| | CMRSA-7 (USA400)/ CMRSA-10 (USA300) | | | Other genotypes | | |
| | No. tested | $MIC_{90}$ (μg/ml) | % resistant | No. tested | $MIC_{90}$ (μg/ml) | % resistant |
| Erythromycin | 1,316 | >8.0 | 80 | 6,626 | >8.0 | 94 |
| Clindamycin | 1,316 | >4.0 | 16 | 6,216 | >4.0 | 91 |
| Tetracycline | 1,316 | ≤2.0 | 3 | 6,565 | >16 | 20 |
| TMP-SMX[a] | 1,316 | ≤0.25 | 1 | 6,626 | >8.0 | 30 |
| Ciprofloxacin | 1,316 | >8.0 | 69 | 6,626 | >8.0 | 93 |
| Gentamicin | 1,269 | 1.0 | 2 | 3,370 | >16 | 13 |
| Rifampin | 1,315 | ≤0.25 | 0.2 | 6,565 | ≤0.25 | 2 |
| Vancomycin | 1,316 | 1.0 | 0 | 6,626 | 1.0 | 0 |
| Fusidic acid[b] | 1,312 | 0.25 | 4 | 6,231 | 0.5 | 6 |
| Mupirocin[c] | 1,315 | >512 | 12 | 6,565 | >512 | 3 |
| Tigecycline | 661 | 0.25 | 0 | 1,292 | 0.5 | 0 |
| Linezolid | 1,275 | 2.0 | 0 | 3,830 | 2.0 | 0 |
| Daptomycin | 661 | 0.5 | 0 | 1,292 | 0.5 | 0 |
| Ceftobiprole | 661 | 1.0 | 0 | 1,292 | 2.0 | 0 |
| Multidrug resistant | 1,316 | | 6 | 2,626 | | 38 |

[a] TMP-SMX, trimethoprim-sulfamethoxazole.
[b] Resistance to fusidic acid defined as exhibiting an MIC of ≥2.0 mg/ml (9).
[c] (High-level) resistance to mupirocin defined as exhibiting an MIC of ≥512 mg/ml (22).

were also less likely to be multidrug resistant (6% of CA-MRSA isolates versus 38% of HA-MRSA isolates; $P < 0.001$).

This study provides the first comprehensive data describing the antimicrobial susceptibilities of a large sample of MRSA isolates from hospitalized patients in Canada. The results suggest that the antimicrobial susceptibilities vary regionally, have evolved over time, and vary depending on the genotype (CA-MRSA versus HA-MRSA). Resistance to erythromycin, clindamycin, and ciprofloxacin was relatively common. However, most isolates were susceptible to tetracycline, trimethoprim-sulfamethoxazole, gentamicin, and rifampin and were uniformly susceptible to newer agents, such as linezolid, daptomycin, tigecycline, and ceftobiprole. We did not identify any strains with reduced susceptibility to vancomycin, and there has been only one prior report of a Canadian isolate with intermediate vancomycin resistance (27). A previous study identified a small number of MRSA isolates with vancomycin heteroresistance (hVISA) in Canada (1), but there has not been any evidence of "MIC creep," as has been reported elsewhere (19, 26).

Similar to results reported in the United States (24), we observed regional differences in the antimicrobial resistance profiles of MRSA. Resistance to certain agents (tetracycline, trimethoprim-sulfamethoxazole, and mupirocin) was more common in the western provinces than in central Canada or the eastern part of the country. In contrast, MRSA isolates from patients hospitalized in western Canada were less likely to be resistant to clindamycin. The reasons for this regional variability are uncertain but may be related to differences in MRSA clonal distribution (most of the CA-MRSA isolates were recovered from patients in western provinces) (20) or to variations in antimicrobial utilization (our study was not able to assess antimicrobial utilization).

Compared to isolates obtained in the first few years of the surveillance, recent MRSA isolates tended to be more susceptible to a variety of oral antimicrobial agents often used to treat less severe MRSA infections. In particular, isolates became increasingly susceptible to clindamycin, tetracycline, and trimethoprim-sulfamethoxazole. The only significant increase in resistance over time was seen with high-level resistance to mupirocin, as previously reported in Canada (23). This change in antimicrobial susceptibilities appeared to be associated with an increase in the proportion of CA-MRSA isolates identified in Canadian hospitals in the past 5 years (5, 20). Community-associated strains were generally more susceptible to antimicrobial agents and much less likely to be multidrug resistant than were HA-MRSA strains, as previously reported in recent U.S. studies (11, 25). However, resistance is likely to increase in CA-MRSA strains, as they become prevalent in health care settings and become subject to increasing antimicrobial selection pressure (13).

This study presents the results of antimicrobial susceptibility testing of a large number of MRSA isolates obtained in prospective surveillance across Canada over 14 years. A limitation of the study is that most of the participating hospitals were tertiary care referral centers, and the results may not be representative of other health care facilities in Canada; they are, however, representative of teaching hospitals in the country.

In conclusion, in the past decade, Canadian MRSA strains have become more susceptible to several classes of non-β-lactam antimicrobial agents. Much of this change is likely attributable to the recent emergence of CA-MRSA strains in Canada. Ongoing surveillance is required to monitor changes in antimicrobial susceptibility profiles, particularly as CA-MRSA strains become prevalent in health care settings.

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