Antibiotic Resistance Trends in Methicillin-Resistant *Staphylococcus aureus* Isolated in Kuwait Hospitals: 2011–2015

Edet E. Udo  Samar S. Boswihi

Department of Microbiology, Faculty of Medicine, Kuwait University, Safat, Kuwait

**Significance of the Study**

- This study revealed changes in the resistance patterns of methicillin-resistant *Staphylococcus aureus* isolates to some antibiotics over time in Kuwait. These findings are significant for empirical antibiotic use and the formulation of antibiotic policy which impacts patient care as well as control and prevention of infections in Kuwait.

**Keywords**

Antibiotic resistance · Methicillin-resistant *Staphylococcus aureus* · Staphylococcal cassette chromosome *mec* typing · Healthcare-associated methicillin-resistant *Staphylococcus aureus* · Community-associated methicillin-resistant *Staphylococcus aureus*

**Abstract**

**Objective:** The aim of this study was to determine antibiotic resistance trends and carriage of staphylococcal cassette chromosome *mec (SCCmec)* genetic elements in methicillin-resistant *Staphylococcus aureus* (MRSA) isolated in Kuwait hospitals to ascertain whether they were healthcare associated (HA-MRSA) or community associated (CA-MRSA). **Materials and Methods:** In total, 6,922 MRSA isolates obtained from different clinical samples were tested for resistance to antibiotics, urease production, and carriage of SCCmec elements. **Results:** All MRSA isolates were susceptible to linezolid, vancomycin, and teicoplanin. However, some isolates were resistant to kanamycin (2,979; 43%), ciprofloxacin (2,955; 42.7%), erythromycin and clindamycin (2,935; 42.4%), fusidic acid (2,858; 41.2%), gentamicin (2,665; 38.5%), tetracycline (2,652; 38.3%), and trimethoprim (2,324; 33.5%). Whereas the prevalence of resistance to most antibiotics showed annual variations, those resistant to chloramphenicol and rifampicin increased from 2.6 and 0.1% to 9.6 and 1.6%, respectively, and high-level mupirocin resistance declined from 9.3% in 2011 to 3.6% in 2015. In total, 3,244 (53.9%) of the isolates carried SCCmec IV followed by SCCmec III (1,737; 28.8%) and SCCmec V (890; 14.8%). SCCmec I (21; 0.3%) and II (79; 0.8%) occurred sporadically. A total of 3,651 (60.7%) of the isolates belonged to the CA-MRSA genotype and 2,290 isolates (38.1%) were identified as HA-MRSA. **Conclusion:** This study demonstrates changes in antibiotic resistance patterns of MRSA over time and reinforces the value of surveillance in detecting such changes for the benefit of infection control and patient management.

© 2017 The Author(s)
Published by S. Karger AG, Basel
Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of healthcare- and community-associated infections worldwide [1]. Since its emergence in UK in 1960s [2], MRSA strains have been isolated from various parts of the world, and the burden of infections caused by them is increasing among different patient populations globally [1, 3]. The MRSA isolates were initially associated with hospitals and other healthcare facilities, such as nursing homes and long-term care facilities [4]. However, in the 1990s, MRSA started to be isolated from apparently healthy individuals in communities who had no previous history of hospital admission or medical treatment [5, 6]. These types of MRSA strains were described as community-acquired, community-originated, community-associated, or community-onset MRSA (CA-MRSA) [7–10]. Since then, CA-MRSA isolates have become major causes of infections in the community and healthcare facilities worldwide [1, 3, 8–10].

Methicillin resistance is mediated by the mecA gene, which confers resistance to all beta-lactam antibiotics, located on a mobile genetic island called staphylococcal cassette chromosome mec (SCCmec). SCCmec types differ in size and structural organizations. These differences in SCCmec types have been used to type MRSA for epidemiological purposes and to distinguish HA-MRSA from CA-MRSA [11, 12]. Currently, 11 SCCmec types have been described [12]. The CA-MRSA strains harbour SCCmec IV, V, and VI, while HA-MRSA strains usually harbour SCCmec I, II, and III [3, 10], except for the UK epidemic MRSA-15 (UK EMRSA-15) which also carries type IV SCCmec, prompting Otter and French [13] to suggest that using SCCmec typing as a marker for CA-MRSA poses a particular problem because the presence of SCCmec IV in successful HA-MRSA lineages such as ST22-SCCmec IV (EMRSA-15) might increase the likelihood that these strains could be misclassified as CA-MRSA. However, EMRSA-15 strains carry a mutation in the UreC gene and therefore do not produce urease [14]. The inability to produce urease is therefore used as a phenotypic marker to distinguish EMRSA-15 isolates carrying SCCmec IV from CA-MRSA [15, 16].

A study of MRSA isolated in Kuwait hospitals from 1992 to 2010 revealed that the MRSA isolates belonged to diverse clones that changed in numbers and type over time with ST239-MRSA-III, a healthcare-associated clone as the dominant MRSA clone in conjunction with the emergence of various CA-MRSA clones [17]. In this study, MRSA isolated between 2011 and 2015 were characterized for susceptibility to antibiotics to detect changes in the prevalence of resistance to those antibiotics overtime. The isolates were also investigated for their carriage of SCCmec genetic elements to ascertain the distribution of HA-MRSA and CA-MRSA genotypes.

Materials and Methods

**MRSA Isolates**

The MRSA isolates were collected as part of routine diagnostic microbiology and submitted to the MRSA Reference Laboratory, located at the Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait, for epidemiological typing. In total, 6,922 MRSA isolates were obtained from patients from January 2011 to December 2015 in 14 public hospitals in Kuwait as shown in Table 1. Most of the MRSA isolates were from patients in Mubarak Al-Kabeer, Al-Amiri, Al-Sabah, Farwanja, Al-Razi, and maternity hospitals. The isolates were identified at the Diagnostic Microbiology laboratories using cultural characteristics, Gram’s stain, and positive tube coagulase and deoxyribonuclease tests. The isolates were preserved in glycerol 15% (v/v) in brain heart infusion broth (BHIB, Oxoid, Basingstoke, UK) at –80°C. The isolates were recovered at the Reference Laboratory by subculturing in BHIB at 37°C for 24 h followed by two further subcultures on brain heart infusion agar.

**Susceptibility to Antimicrobial Agents**

The disk diffusion method was used [18] to determine susceptibility to antimicrobial agents on Mueller-Hinton Agar (Oxoid, UK) using the following antibiotic disks (Oxoid): benzyl penicillin (2 U), cefoxitin (30 μg), kanamycin (30 μg), mupirocin (200 μg), gentamicin (10 μg), erythromycin (15 μg), clindamycin (2 μg), chloramphenicol (30 μg), tetracycline (10 μg), trimethoprim (2.5 μg), fusidic acid (10 μg), rifampicin (5 μg), ciprofloxacin (5 μg), and linezolid (30 μg). The minimum inhibitory concentration (MIC) of cefoxitin, vancomycin, and teicoplanin were determined with Etest strips (BioMerieux, Marcey L’Etoile, France) according to the manufacturer’s instructions [18]. *S. aureus* strain ATCC 25923 was used as the quality control strain for susceptibility testing. Methicillin resistance was confirmed by detecting PBP 2a using a rapid latex agglutination kit (Denka-Seiken, Japan) according to the manufacturer’s instructions.

**Urease Production**

Urease production was detected on Christensen’s urea agar slope after 24 h of incubation at 35°C. All isolates that carried SCCmec IV genetic element were tested for urease production to distinguish between EMRSA-15 and CA-MRSA isolates.

**SCCmec Typing**

SCCmec typing was performed on all the MRSA isolates obtained from 2012 to 2015 for the carriage of SCCmec types I, II, III, IV, and V using the protocol described by Zhang et al. [19]. SCCmec typing was not performed on MRSA isolates in 2011.
Results

Overall, the number of MRSA isolated annually demonstrated an increasing trend for all the hospitals (Table 1). The skin and soft tissues (2,835; 40.9%) as well as nasal swabs (1,606; 23.2%) were the major sources of MRSA isolates followed by ETS, blood, and throat swabs (Table 2). The clinical sites for 435 (6.2%) of the MRSA isolates were not reported.

Antibiotic Susceptibility of MRSA Isolates

The 5-year cumulative prevalence of resistance to non-beta-lactams antibiotics for the MRSA isolates is shown in Table 3. All the isolates were susceptible to linezolid, while 2,623 (99.4%) of the isolates were susceptible to rifampicin. Overall, 2,979 (43%) of the MRSA isolates were resistant to kanamycin. Resistance to other antibiotics is shown in Table 3. MIC determination for vancomycin and teicoplanin showed that 6,828 (98.7%) of the isolates were susceptible to vancomycin (MIC: ≤2 μg/mL), while 94 (1.3%) had vancomycin with MIC values of 3 μg/mL. None of the isolates expressed vancomycin MIC of ≥4 μg/mL. In total, 6,730 (97.2%) of the isolates were susceptible to teicoplanin (MIC: ≤2 μg/mL) and 180 isolates (2.6%) expressed MIC of 3 μg/mL, while 12 isolates (0.2%) had MIC of 4 μg/mL.

Table 1. Sources of methicillin-resistant *Staphylococcus aureus* isolates in Kuwait hospitals: 2012–2015

| Hospitals  | 2011 | 2012 | 2013 | 2014 | 2015 | Total |
|------------|------|------|------|------|------|-------|
| MBH        | 240  | 249  | 290  | 411  | 481  | 1,671 (24.1) |
| AMH        | 2    | 91   | 142  | 210  | 121  | 566 (8.1) |
| ARH        | 91   | 88   | 99   | 138  | 118  | 534 (7.7) |
| JH         | 65   | 67   | 65   | 102  | 49   | 348 (5.0) |
| ASH        | 194  | 182  | 257  | 178  | 311  | 1,122 (16.2) |
| IBS        | 70   | 98   | 70   | 25   | 23   | 286 (4.1) |
| FAW        | 64   | 101  | 156  | 176  | 91   | 588 (8.5) |
| CDH        | 23   | 30   | 49   | 97   | 180  | 379 (5.4) |
| MAT        | 152  | 191  | 185  | 232  | 270  | 1,030 (14.8) |
| Others¹    | 5    | 111  | 74   | 81   | 127  | 398 (5.7) |
| Total      | 906  | 1,208| 1,387| 1,650| 1,771| 6,922 (100) |

Values are presented as n (%). MBH, Mubarak Al-Kabeer Hospital; AMH, Al-Amiri Hospital; ARH, Al-Razi Hospital; JH, Al-Jarah Hospital; ASH, Al-Sabah Hospital; IBS, Ibn-Sina Hospital; FAW, Farawriya Hospital; CDH, chest disease hospital; MAT, maternity hospital. ¹ Others include Adan Hospital, KOC Hospital, and military, allergy, and infectious diseases hospitals.

Table 2. Clinical samples for methicillin-resistant *Staphylococcus aureus* isolates: 2012–2015

| Clinical sample     | 2011 | 2012 | 2013 | 2014 | 2015 | Total |
|---------------------|------|------|------|------|------|-------|
| Skin and soft tissues | 365  | 675  | 513  | 772  | 510  | 2,835 (40.9) |
| Nasal swabs         | 193  | 218  | 329  | 341  | 525  | 1,606 (23.2) |
| Blood               | 38   | 30   | 52   | 94   | 92   | 306 (4.4) |
| Urine               | 3    | 24   | 26   | 38   | 28   | 119 (1.7) |
| Throat swabs        | 70   | 54   | 25   | 63   | 58   | 270 (3.9) |
| Ear swabs           | 16   | 19   | 22   | 13   | 46   | 116 (1.6) |
| ETS                 | 49   | 65   | 61   | 35   | 123  | 333 (4.8) |
| Miscellaneous¹      | 66   | 31   | 307  | 203  | 295  | 902 (13.0) |
| Not specified        | 106  | 92   | 52   | 91   | 94   | 435 (6.2) |
| Total               | 906  | 1,208| 1,387| 1,650| 1,771| 6,922 (100) |

Values are presented as n (%). ETS, endotracheal swab. ¹ High vaginal swabs, sputum, fluids, axilla, groins, eye swabs, and catheter tips.
Antibiotic Resistance Trends: 2011–2015

Resistance trends to non-beta-lactam antibiotics in MRSA strains from 2011 to 2015 are presented in Table 3. From 2011 to 2014, the prevalence of resistance to aminoglycosides represented by gentamicin and kanamycin decreased from 44.3% and 53.4% to 31.2% and 36.8%, respectively. This was followed by an increase in resistance to these antibiotics in 2015 to 39.6% for gentamicin and 42.9% for kanamycin. A similar trend was observed for ciprofloxacin, which decreased from 52.2% in 2012 to 33.4% in 2014 with an increase of 51.2% in 2015. The proportion of MRSA isolates that were resistant to erythromycin and clindamycin declined in 2012 (43.8%) compared to 2011 (51.3%), and appeared to stabilize from 2013 (41.2%) to 2015 (40.5%).

The prevalence of resistance to fusidic acid declined in 2012 (424; 35.0%) compared to 2011 (411; 45.3%), but increased gradually from 519 (37.4%) in 2013 to 853 (48.1%) in 2015. The prevalence of resistance to tetracycline declined from 493 (40.8%) in 2012 to 493 (34.5%) in 2013, but showed a slight increase in 2014 (601; 36.4%) and 2015 (629; 35.5%). The proportion of MRSA strains resistant to trimethoprim declined between 2011 (304; 33.5%) and 2013 (417; 30.0%), but increased in 2014 (571; 34.6%) and 2015 (654; 36.9%) to surpass the level of 2011. The number of MRSA strains expressing high-level resistance to mupirocin showed a declining trend from 85 (9.3%) in 2011 to 50 (3.6%) in 2013, and increased slightly to 66 (4.0%) in 2014. In contrast, the proportion of strains that were resistant to chloramphenicol increased.

Table 3. Antibiotic resistance of methicillin-resistant Staphylococcus aureus isolates: 2012–2015

| Antibiotics       | 2011 (%) | 2012 (%) | 2013 (%) | 2014 (%) | 2015 (%) | Total (%) |
|-------------------|----------|----------|----------|----------|----------|-----------|
| Gentamicin        | 402 (44.3) | 549 (45.4) | 496 (35.7) | 516 (31.2) | 702 (39.6) | 2,665 (38.5) |
| Kanamycin         | 484 (53.4) | 594 (49.1) | 532 (38.3) | 608 (36.8) | 761 (42.9) | 2,979 (43.0) |
| Erythromycin      | 465 (51.3) | 529 (43.8) | 572 (41.2) | 651 (39.4) | 718 (40.5) | 2,935 (42.4) |
| Clindamycin       | 465 (51.3) | 529 (43.8) | 572 (41.2) | 651 (39.4) | 718 (40.5) | 2,935 (42.4) |
| Chloramphenicol   | 24 (2.6) | 51 (4.2) | 55 (3.9) | 130 (7.8) | 171 (9.6) | 431 (6.2) |
| Tetracycline      | 450 (49.6) | 493 (40.8) | 479 (34.5) | 601 (36.4) | 629 (35.5) | 2,652 (38.3) |
| Trimethoprim      | 304 (33.5) | 378 (31.3) | 417 (30.0) | 571 (34.6) | 654 (36.9) | 2,324 (33.5) |
| Fusidic acid      | 411 (45.3) | 424 (35.0) | 519 (37.4) | 651 (39.4) | 853 (48.1) | 2,858 (41.2) |
| Ciprofloxacin     | 473 (52.2) | 520 (43.0) | 507 (36.5) | 551 (33.4) | 904 (51.0) | 2,955 (42.7) |
| Mupirocin HL      | 85 (9.3) | 85 (7.0) | 50 (3.6) | 66 (4.0) | 65 (3.6) | 351 (5.0) |
| Rifampicin        | 1 (0.1) | 7 (0.5) | 2 (0.1) | 2 (0.1) | 30 (1.6) | 42 (0.6) |

Values are presented as n (%).

Table 4. Distribution of SCCmec elements in methicillin-resistant Staphylococcus aureus isolates: 2012–2015

| SCCmec types | 2012 (n = 1,208) | 2013 (n = 1,387) | 2014 (n = 1,650) | 2015 (n = 1,771) | Total (n = 6,016) |
|--------------|-----------------|-----------------|-----------------|-----------------|------------------|
| I            | 5               | 7               | 5               | 4               | 41 (0.3)         |
| II           | 6               | 34              | 4               | 5               | 49 (0.8)         |
| III          | 364             | 398             | 384             | 591             | 1,737 (28.8)    |
| IV           | 570             | 798             | 964             | 912             | 3,244 (53.9)    |
| EMRSA-15     | 63              | 147             | 129             | 147             | 483 (8.0)       |
| V            | 235             | 145             | 269             | 221             | 890 (14.8)      |
| ND           | 28              | 5               | 4               | 38              | 75 (1.2)        |
| HA-MRSA      | 438             | 586             | 522             | 744             | 2,290 (38.1)    |
| CA-MRSA      | 742             | 796             | 1,124           | 989             | 3,651 (60.7)    |

Values are presented as n (%). EMRSA-15, epidemic MRSA-15; ND, not determined; HA-MRSA, healthcare-associated MRSA; CA-MRSA, community-associated MRSA; SCCmec, staphylococcal cassette chromosome mec.
steadily from 24 (2.6%) in 2011 to 130 (7.8%) in 2014 and 171 (9.6%) in 2015.

**SCCmec Typing of MRSA Isolates**

The distribution of the SCCmec elements is presented in Table 4, indicating that 3,244 (53.9%) of the isolates carried SCCmec type IV. A total of 483 (8.0%) isolates were negative for urease production and were classified as EMRSA-15. The proportions of MRSA isolates carrying the CA-MRSA genotype was higher than those carrying HA-MRSA genotypes (Table 4).

**Discussion**

This study revealed an increasing trend in the number of MRSA isolates obtained annually in Kuwait public hospitals. This is of concern because MRSA limits the choices of antibiotics available for treating infections caused by them, often warranting the use of more expensive antibiotics [20, 21]. The majority (40.9%) of the isolates in this study originated from skin and soft tissue infections concurring with the findings of a previously published study [22]. The results also mimicked the findings of a surveillance study conducted in 2005 in Kuwait hospitals [23] and two studies conducted in the USA and Canada [20, 24] where skin and soft tissues were the major sources of MRSA isolates. In contrast to the findings of this study, lower respiratory tract samples were the major sources accounting for 40.6% of MRSA isolates obtained during an Italian national survey conducted in 2012 [25]. These findings highlight the geographical differences in the epidemiology of MRSA colonization and/or infection.

The observation that all MRSA isolates were susceptible to linezolid is similar to reports from other countries that MRSA isolates were susceptible to linezolid [20, 22, 25]. In addition, the MIC distribution of the glycopeptide antibiotics showed that the majority (~97%) of the isolates were susceptible to vancomycin and teicoplanin (MIC: ≤2 μg/ml), confirming that vancomycin and teicoplanin remain viable options for treating MRSA infections in Kuwait. Similarly, the low prevalence of high-level mupirocin resistance in this study (3.6–9.3%) is a positive development because it preserves the usefulness of mupirocin for nasal decolonization, treatment of skin infections, and prevention of postsurgical wound infections [26, 27]. The results of this study also revealed that the prevalence of resistance to fusidic acid changed from 45.3% in 2011 to 35.0% in 2012 and then increased to 48.1% in 2015, while the prevalence of chloramphenicol resistance increased from 2.6% in 2011 to 9.6% in 2015. These changes in antibiotic resistance patterns probably reflected changes in the genotypes of MRSA circulating in Kuwait hospitals. For example, the increase of resistance to fusidic acid might be due to the increase of the CA-MRSA genotype, ST80-IV-MRSA, characteristically resistant to fusidic acid, in Kuwait hospitals [17].

We observed that 53.9 and 14.8% of the MRSA isolates carrying SCCmec IV and SCCmec V genetic elements, respectively, were identified as CA-MRSA and 28.8% of the isolates carrying SCCmec III were identified as HA-MRSA. These findings are similar to reports in different countries including Switzerland [28], India [29], and Singapore [30], which showed that CA-MRSA strains carrying SCCmec IV and SCCmec V have emerged as dominant MRSA strains in healthcare centers. Until 2010, HA-MRSA strains carrying SCCmec III (belonging to ST239-III-MRSA clone) were the dominant MRSA clone in Kuwait hospitals [17]. Therefore, the presence of CA-MRSA in 60.7% of the MRSA isolates indicates that CA-MRSA has overtaken HA-MRSA isolates as the leading cause of infections and/or colonization in Kuwait hospitals.

**Conclusion**

In this study, the number of MRSA isolates with CA-MRSA genotypes increased steadily from 2011 to 2015. The isolates were susceptible to linezolid, vancomycin, and teicoplanin with low prevalence of resistance to rifampicin, mupirocin, and chloramphenicol. Whereas the prevalence of resistance to some antibiotics varied between 2011 and 2015, that of fusidic acid and chloramphenicol increased and that of high-level mupirocin resistance declined. These results highlight the importance of regular surveillance in detecting changes in antibiotic resistance. Knowledge of changes in antibiotic resistance pattern has an impact on empiric antibiotic prescription, formulation of antibiotic policy, infection control, and patient management.

**Acknowledgments**

We are grateful to the diagnostic microbiology laboratories for submitting the MRSA isolates.
References

1 Deurenberg RH, Stoberingh EE: The evolution of *Staphylococcus aureus*. Infect Genet Evol 2008;8:747–763.
2 Jevon MP: “Celbenin”-resistant staphylococci. Br Med J 1961;1:124–125.
3 Mediavilla JR, Chen L, Mathema B, et al: Global epidemiology of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA). Curr Opin Microbiol 2012;15:588–595.
4 Chambers HF: The changing epidemiology of methicillin-resistant *Staphylococcus aureus*. Emerg Infect Dis 2001;7:178–182.
5 Udo EE, Pearman JW, Grubb WB: Genetic analysis of community isolates of methicillin-resistant *Staphylococcus aureus* in Western Australia. J Hosp Infect 1993;25:97–108.
6 Herold BC, Immergluck LC, Maranan MC, et al: Community-acquired methicillin-resistant *Staphylococcus aureus*: an emerging pathogen. Infect Control Hosp Epidemiol 2003;24:451–455.
7 Wannet WJ, Spalburg E, Heck ME, et al: Emergence of virulent methicillin-resistant *Staphylococcus aureus* strains carrying Panton-Valentine leukocidin genes in the Netherlands. J Clin Microbiol 2005;43:3341–3345.
8 David MZ, Daum RS: Community-acquired methicillin-resistant *Staphylococcus aureus*: epidemiology and clinical consequences of an emerging epidemic. Clin Microbiol Rev 2010;23:616–687.
9 Zetola N, Francis JS, Nueremberger EL, et al: Community-acquired methicillin-resistant *Staphylococcus aureus*: an emerging threat. Lancet Infect Dis 2005;5:275–286.
10 Chongtrakool P, Ito T, Ma XX, et al: Staphylococcal cassette chromosomemec (SCCmec) typing of methicillin-resistant *Staphylococcus aureus* strains isolated in 11 Asian countries: a proposal for a new nomenclature for SCCmec elements. Antimicrob Agents Chemother 2006;50:1001–1012.
11 Liu J, Chen D, Peters BM, et al: Staphylococcal chromosomal cassettes mec (SCCmec): a mobile genetic element in methicillin-resistant *Staphylococcus aureus*. Microb Pathog 2016;101:56–67.
12 Otter JA, French GL: Community-associated methicillin-resistant *Staphylococcus aureus*: the case for a genotypic definition. J Hosp Infect 2012;81:143–148.
13 Holden MT, Huo Y, Kurt K, et al: A genomic portrait of the emergence, evolution, and global spread of a methicillin-resistant *Staphylococcus aureus* pandemic. Genome Res 2013;23:653–664.
14 Richardson JF, Reith S: Characterization of a strain of methicillin-resistant *Staphylococcus aureus* (EMRSA-15) by conventional and molecular methods. J Hosp Infect 1993;25:45–52.
15 Udo EE, Al-Sweih N, Noronha B: Characterisation of non-multiresistant methicillin-resistant *Staphylococcus aureus* (including EMRSA-15) in Kuwait hospitals. Clin Microbiol Infect 2006;12:262–269.
16 Boswili SS, Udo EE, Al-Sweih N: Shifts in the clonal distribution of methicillin-resistant *Staphylococcus aureus* in Kuwait hospitals: 1992–2010. PLoS One 2016;11:e016274.
17 Clinical and Laboratory Standard Institute (CLSI): Performance standards for antimicrobial susceptibility testing; Twenty-Second Informational Supplement. CLSI Document M100-S22 2012;32:1–184.
18 Zhang K, McClure JA, Elsayed S, et al: Novel multiplex PCR assay for characterization and concomitant subtyping of staphylococcal cassette chromosome mec type I to V in methicillin-resistant *Staphylococcus aureus*. J Clin Microbiol 2005;43:5026–5033.
19 Simor AE, Williams V, McGee A, et al: Prevalence of colonization and infection with methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant Enterococcus and *Clostridium difficile* infection in Canadian hospitals. Infect Control Hosp Epidemiol 2013;34:687–693.
20 Farbman I, Avni T, Rubinovitch B, et al: Cost-benefit of infection control interventions targeting methicillin-resistant *Staphylococcus aureus* in hospitals: systemic review. Clin Microbiol Infect 2013;19:ES82–ES93.
21 Olaniyi R, Pozzi C, Grimaldi L, et al: *Staphylococcus aureus*-associated skin and soft tissue infections: anatomical localization, epidemiology, therapy and potential prophylaxis; in Compans RW, Hojio T, Malissen B, Aktories K, Rappuoli R, Galan JE, Ahmed R, Palme K, Casadevall A, Garcia-Sastre A (eds): Current Topics in Microbiology and Immunology. Springer, Berlin, 2016, pp 1–29.
22 Udo EE, Al-Sweih N, Dhar R, et al: Surveillance of antibacterial resistance in *Staphylococcus aureus* in Kuwait hospitals. Med Princ Pract 2008;17:71–75.
23 Wetzel ME, Fleischer AB: Factors affecting the rise of treatment of resistant bacteria in skin and soft tissue infections in the United States: 1993 to 2012. J Dermatol Treat 2016;4:1–17.
24 Campanile F, Bongiorno D, Perez M, et al: Epidemiology of *Staphylococcus aureus* in Italy: first nationwide survey, 2012. J Glob Antimicrob Resist 2015;3:247–254.
25 Laupland KB, Conly JM: Treatment of *Staphylococcus aureus* colonization and prophylaxis is for with topical intranasal mupirocin: an evidence-based review. Clin Infect Dis 2003;37:933–938.
26 Engelman R, Shahian D, Shemin R, et al: The Society of Thoracic Surgeons practice guidelines series: antibiotic prophylaxis in cardiac surgery. II. Antibiotic choice. Ann Thorac Surg 2007;83:1569–1576.
27 Valsecia G, Rossi M, Bertschy S, et al: Emergence of SCCmec type IV and SCCmec type V methicillin-resistant *Staphylococcus aureus* containing the Panton-Valentine leukocidin genes in a large academic teaching hospital in central Switzerland: external invaders or persisting circulators? J Clin Microbiol 2010;48:720–727.
28 Dhawan B, Rao C, Udo EE, et al: Dissemination of methicillin-resistant *Staphylococcus aureus* SCCmec type IV and SCCmec type V epidemic clones in a tertiary hospital: challenge to infection control. Epidemiol Infect 2015;143:343–353.
29 Udo EE: Community-acquired methicillin-resistant *Staphylococcus aureus*: the new face of an old foe? Med Princ Pract 2013;22:20–29.