Methicillin-resistant *Staphylococcus aureus*: a systematic review

Mohammad Reza Nazari[a], Zamberi Sekawi[b], Nourkhoda Sadeghifard[a], Mohammad Raftari[b] and Sobhan Ghafourian[a]

Staphylococcus aureus is a Gram-positive facultative aerobic, nonmotile coccus that is an opportunistic pathogen in both humans and animals. A new window was opened for eradication of infections by bacteria with the discovery of antibiotics. Plasmid-borne resistance genes appeared soon afterwards. Currently, the distribution of antibiotic-resistant genes between bacteria via horizontal and vertical transformation and prescription of antibiotics has severely complicated treatment of infection. Antibiotic resistant bacteria have become a worldwide concern. Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Staphylococcus aureus* are now recognized as problematic bacteria. The current review aims to cover some aspects of MRSA and its distribution worldwide.

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Keywords: methicillin-resistant *Staphylococcus aureus*, *Staphylococcus aureus*, vancomycin-resistant *Staphylococcus aureus*

Introduction

Staphylococcus aureus is a Gram-positive coccus, facultative aerobic, and grows as grape-like clusters; it is an opportunistic pathogen for both humans and animals. The most common infections by *S. aureus* are skin and soft tissue infections, respiratory infections and food poisoning [1].

Carriage of *Staphylococcus aureus*

Naturally, *S. aureus* colonizes humans and can be found in the throat, perineum, groin, anterior nares and skin. Nasal carriage of *S. aureus* is one of the common risk factors causing infections in the community and in hospitals [2,3]. Nasal carriage of *S. aureus* is associated with infection in patients with underlying diseases including AIDS, insulin-dependent diabetes mellitus, continuous ambulatory peritoneal dialysis and skin diseases [4,5].

Prevalence of *S. aureus* nasal carriage varies from 9 to 100%, with a mean of 37% [6]. *S. aureus* nasal carriage rates varied with the age of the human individual [3,6]; there is higher rate of *S. aureus* nasal carriage among children than among adults. It is more prevalent between the ages of 10 and 20 years [7]. In addition, the rate of *S. aureus* nasal carriage was found to be higher in boys than in girls and is therefore associated with the hormonal status [8]. Different strains of *S. aureus* can be found in the colonized individual potentially stimulating the horizontal transfer of antimicrobial-resistant genes [9].

Staphylococcus aureus infections

S. aureus causes many diseases in humans, including skin and soft tissue infections (abscesses, carbuncles, folliculitis, furuncles, impetigo, bullous impetigo and cellulitis), which in the absence of antimicrobial therapy may lead to

[a]Clinical Microbiology Research Center, Ilam University of Medical Sciences, Ilam, Iran, and the [b]Department of Medical Microbiology and Parasitology, Faculty of Medicine and Health Sciences, University Putra Malaysia, Selangor, Malaysia.

Correspondence to Sobhan Ghafourian, PhD, Clinical Microbiology Research Center, Ilam University of Medical Sciences, 6931619 Ilam, Iran.

E-mail: sobhanghafurian@yahoo.com

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bloodstream infections and septic shock [10]. Other infections caused by *S. aureus* include endocarditis, pneumonia, bone and joint infections. *S. aureus* skin infections are frequent in the United States, Canada, Latin America, Europe and the Western Pacific, although it is isolated from cases of pneumonia and bloodstream infection worldwide [11]. Wound and catheter-related infections are closely associated with *S. aureus*. One primary cause of nosocomial bacteraemia is associated with intravascular catheter-related infections [12]. Toxin-mediated diseases such as toxic shock syndrome and food poisoning are associated with TSST-1 and enterotoxin-producing *S. aureus* [13].

Methicillin-resistant *Staphylococcus aureus*

History of methicillin-resistant *Staphylococcus aureus*

The 1940s saw the introduction of penicillin, the first antimicrobial agent effective against *S. aureus*. Subsequently, resistance to penicillin was observed [14] and a plasmid harbouring β-lactamase gene was found to be responsible for creation of penicillin-resistant *S. aureus* [15]. Penicillin-resistant *S. aureus* became a worldwide concern during the next two decades. In 1959, methicillin (a semi-synthetic derivative of penicillin and resistant to the β-lactamase enzyme) was used for treatment of infections caused by penicillin-resistant *S. aureus*. After that, penicillin-resistant *S. aureus* decreased significantly [16]. The first isolates of methicillin-resistant *S. aureus* (MRSA) were reported in 1961 [17]. Until the late 1970s, the prevalence of MRSA was considered sporadic, but MRSA was soon observed worldwide [18]. MRSA is now a major cause of morbidity and mortality [19], and increasingly prevalent in many regions [20].

Mechanism of resistance to methicillin in *Staphylococcus aureus*

Penicillin-binding proteins: the targets of β-lactam antibiotics

Peptidoglycan structure in *Staphylococcus aureus* The *S. aureus* cell wall comprises a very thick layer of peptidoglycan. The structure of the cell wall is a repeat of β1–4-linked N-acetylglucosamine-N-acetylmuramic acid (NAM) with attached teichoic acids [21]. Each NAM is cross-linked to four of five amino acid chains containing L-alanine, D-iso-glutamine, L-lysine and D-alanine with a penta-glycine bridge between L-Lysine and D-alanine (Fig. 1).

The bridge is formed in the cytoplasm by FemX, FemA and FemB proteins that bind the glycine residues to the L-lysine residue of the stem peptides. The cross-linking occurs on the external layer of the cytoplasmic membrane in a reaction catalyzed by penicillin-binding proteins (PBPs). The PBPs are divided into four types, namely PBP1, PBP2, PBP3 and PBP4.

The PBPs have two protein domains, one of the domains is in cross-linking and another in transglycosylation. β-lactam antibiotics such as methicillin and oxacillin bind to the terminal D-alanyl-D-alanine of the stem peptide, thereby inhibiting the first domain of PBPs (transpeptidation) and the initiation of cross-linking. Therefore, the peptidoglycan is unable to crosslink, allowing leakage of cytoplasm outside the cell, resulting in the death of the bacterial cells [22]. MRSA has developed a different foreign PBP called PBP2a (resistant to methicillin).

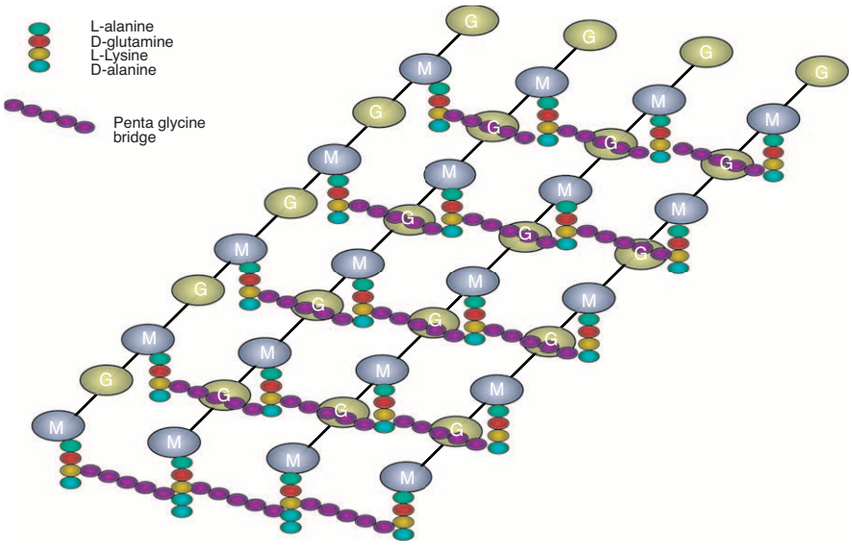

Fig. 1. Peptidoglycan structure of *Staphylococcus aureus*.

Penicillin-binding protein 2a

The difference between methicillin-sensitive *S. aureus* and MRSA is the presence of *mecA* gene, which encodes a different 78-kDa PBP (PBP2a). The *mecA* gene is originally from *Staphylococcus sciuri* [23]. CcrA and B, located in *mec* element, code a recombinase protein that is responsible for unifying and fission of the *mec* element into the chromosome [24]. The *mec* element is highly conserved between different isolates. PBP2a is a motif from the other PBP, which has a low affinity to bind with β-lactam antibiotics. Notably, resistance to methicillin and other β-lactam antibiotics in *S. aureus* is associated with mobile staphylococcal chromosomal cassettes that harbour the *mec*A gene and is known as Staphylococcal chromosomal cassettes *mecA* (SCC*mecA*) [24].

*The **ccr** gene complex*

The *ccr* gene complex includes the *ccr* genes and ORFs. *S. aureus* has three different *ccr* genes, which are *ccrA, B* and *C. CcrA* and *B* are divided into four different allotypes. *Ccr* genes, which have more than 85% similarity in their sequences, are classified as the same allotype. The *ccrC* gene has more than one different allele, *ccrC1* allele 2, *ccrC1* allele 3. Different *ccr* have different allotypes; for example, *S. aureus* type 1 harboured ccrA1B1 and type 2 possesses ccrA2B2 [25].

mecA

As mentioned, *mecA* is associated with resistance to the *β*-lactam antibiotics. *mecA* encodes PBP2a, which is different from the other PBPs [26]. *MecI* and *mecR1* are the regulator genes that control *mecA. MecI* is the repressor for *mecA*, while *mecR1* plays a different role as a signal for transduction cascade [27]. In addition, *mecA* is also under control of two corepressors (*blaI* and *blaR1*). *BlaI* is homologous of *mecI* and *blaR1* is similar to *mecR1*. These two corepressors are responsible for controlling *blaZ* that is responsible for penicillin resistance [26]. Also, *blaI* is able to bind to *mecA* operator and suppress the transcription of *mecA* [28].

*Staphylococcal cassette chromosome **mec***

Staphylococcal cassette chromosome *mec* (SCC*mec*) is known as a genomic island of unknown origin, as it has the antimicrobial resistance gene *mecA* [26]. SCC*mec* also has other genes including *ccrA* and *ccrB,* which code the recombinase proteins for incorporation and fission of the SCC*mec* elements from *S. aureus* chromosome [26]. SCC*mec* elements are divided into different types with various *mec* and *ccr* genes. These different SCC*mec* elements cause variation of antimicrobial resistance and different kinds of infections [29]. Types I–III SCC*mec* are large elements, which possess other antimicrobial resistance genes and are found in community-associated MRSA and hospital-associated MRSA (CDC, 2007). On the contrary, types IV and V are found more in community-associated MRSA [29].

In all types, the integration occurs in the attBscc site near to the origin of the replication of *S. aureus* [30]. There are three classes of *mec* as follows: class A *mec* contains two *mecI* (transcriptional repressor protein) and *mecR1* (signal transduction protein) genes [31], while class B *mec* includes *mecA* (with deletion of *mecI* and some parts of mecR1) and insertion sequence 1272 that are incorporated into the deletion site of *mecA*. Class C2 contains two copies of insertion sequence 431, *mecA* (short mecR1) [32]. Thus, type I SCC*mec* harbours class B *mec* and ccrA; type II SCC*mec* has class A *mec* and *ccrB*; type III SCC*mec* contains class A *mec* and type *ccrC*; type IV carries class B *mec* and type *ccrB*; and type V possess class C *mec* and type 5 *ccr*. Therefore, naming of a new *SCCmec* type is based on *ccr* complex and class of *mec* gene.

Public health importance

MRSA is one of the most important antibiotic-resistant pathogens. There is an increasing prevalence of MRSA worldwide. ICUs in the United States showed an increase in MRSA from 36% in 1992 to 64.5% in 2003 [33]. In Europe, the prevalence ranges from 1 to 50%. The morbidity and mortality caused by MRSA infections in the UK increased during the period 1993–2005 (National Statistics, 2007). In 2012, a meta-analysis study in Iran showed that the prevalence of MRSA ranged from 20.4% in Isfahan to 90% in Tehran. Infections by MRSA lead to longer term hospitalization and higher care costs [34].

Surveillance programmes appear to be necessary, such as the European Antibiotic Resistance Surveillance System (EARSS), which monitors the seven most invasive bacteria responsible for antimicrobial resistance (www.earss.rivm.nl). Currently, one of the most crucial issues is the presence of MRSA in the community. In 1993, Australia reported the prevalence of the first MRSA in the community [35]. This was followed by reports of four MRSA in the community, causing paediatric deaths. Now, the prevalence of MRSA in the community is reported worldwide [36], representing a change in the epidemiology of community-associated and hospital-associated MRSA worldwide.

Epidemiology

It is estimated that the range of distribution of MRSA is between 23 and 73% worldwide. MRSA is found to be an important cause of skin and respiratory infections [11]. Malaysia showed a high prevalence of MRSA in 1996 [37]; MRSA were found in the surgical wards and linked to the use of invasive procedures [38].

Europe

It is estimated that the prevalence of MRSA in Europe is around 26% currently. In the SENTRY programme between 1997 and 1999, European countries showed variance in the frequency of prevalence of MRSA (Fig. 2). These surveys revealed greater prevalence in

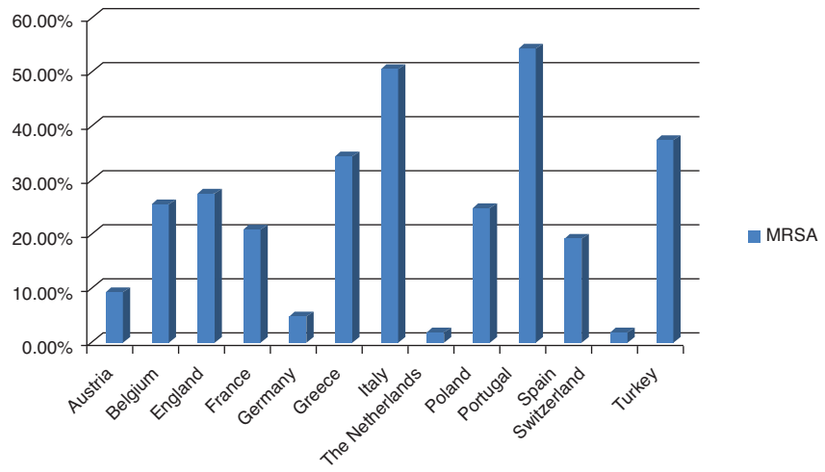

Fig. 2. Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in different European countries as SENTRY centres, 1997–1999 [11].

southern Europe [11]. Tiemersma *et al.* [39] revealed the prevalence of MRSA during the period 1999–2002 in Belgium, Germany, Ireland, Netherlands and the UK. The prevalence of MRSA was varied from 1% in northern Europe to 40% in southern Europe.

Africa

In 1978, the first MRSA was reported in Africa. Thereafter, the occurrence has ranged from 5 to 45% [11,37]. The first isolation of MRSA in Sudan was reported in 1999 [40]. Figure 3 shows the prevalence of MRSA in different African countries.

Asia

The prevalence of MRSA in the Asia Pacific region is greater than in other parts of Asia with a frequency of more than 60%. In Malaysia, the prevalence of MRSA was 17% in 1986 increasing to 40% in 2000 [11]. Figure 4 shows the prevalence of MRSA in the Pacific region.

The United States

In 1974, it was 2%, in 1995, it was 22% and in 2004, it was reported to be 64%. According to the CDC report, 1.5% of the populations of the USA were carriers of MRSA between 2003 and 2004. There was a 50–70% increase in

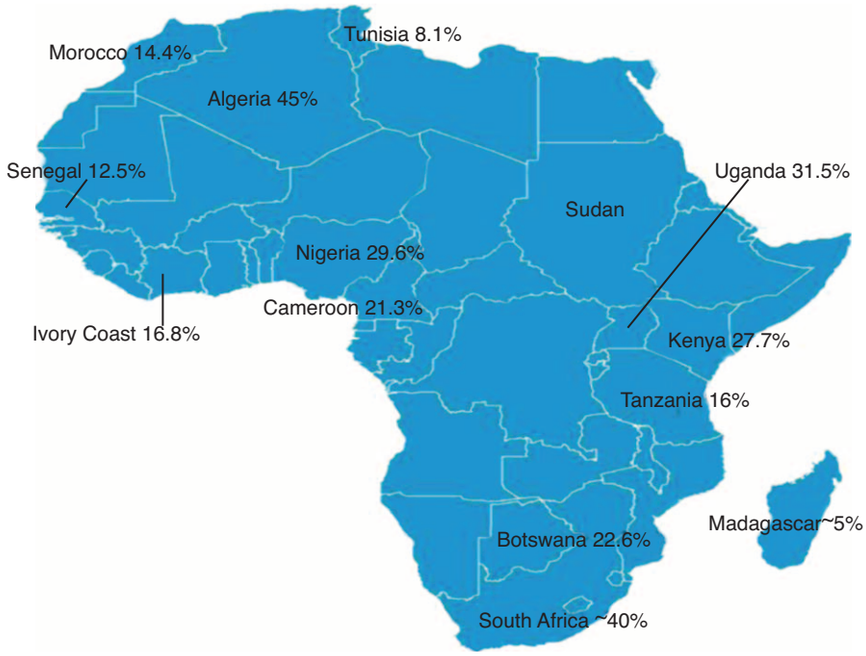

Fig. 3. Prevalence of methicillin-resistant *Staphylococcus aureus* in different countries in Africa [11].

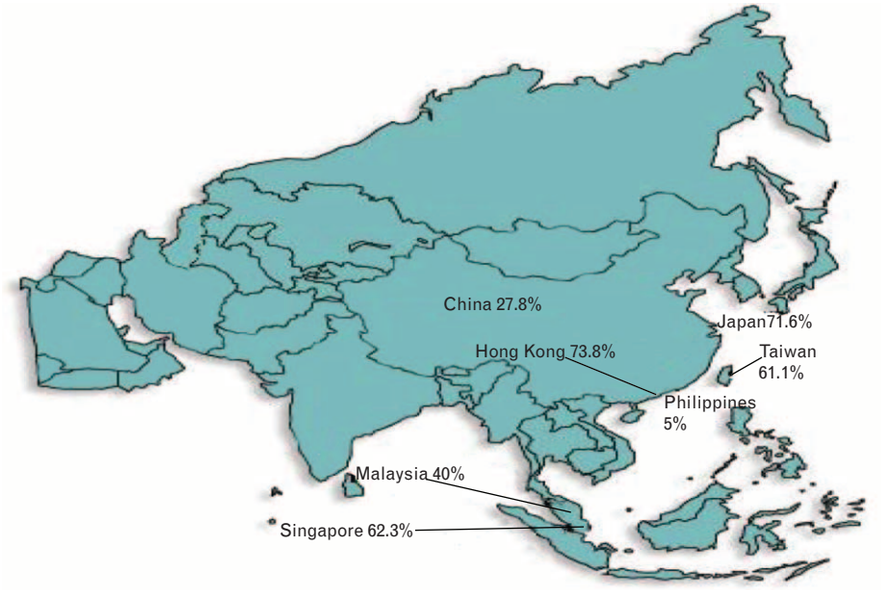

Fig. 4. Prevalence of methicillin-resistant *Staphylococcus aureus* in different countries in the Asia Pacific region [11].

MRSA during the period 2001–2007 in bloodstream infections [41].

Australia

The first report of MRSA in Australia was observed in the 1960s. The first gentamicin-resistant MRSA was found in 1976. Figure 5 shows the prevalence of multiresistant MRSA and nonmultiresistant MRSA in different parts of Australia.

Latest evidence worldwide shows that the highest rate of prevalence (>50%) is in North and South America and

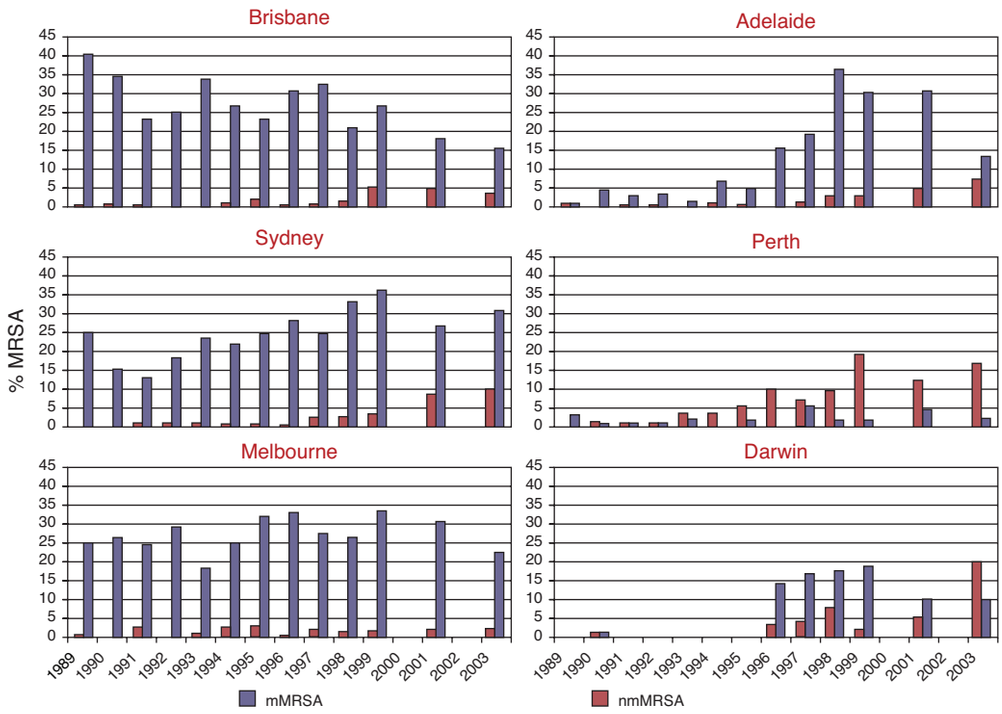

Fig. 5. Prevalence of multiresistant methicillin-resistant *Staphylococcus aureus* (mMRSA) and nonmultiresistant methicillin-resistant *Staphylococcus aureus* in different cities (nmMRSA) in Australia. MRSA, methicillin-resistant *Staphylococcus aureus*.

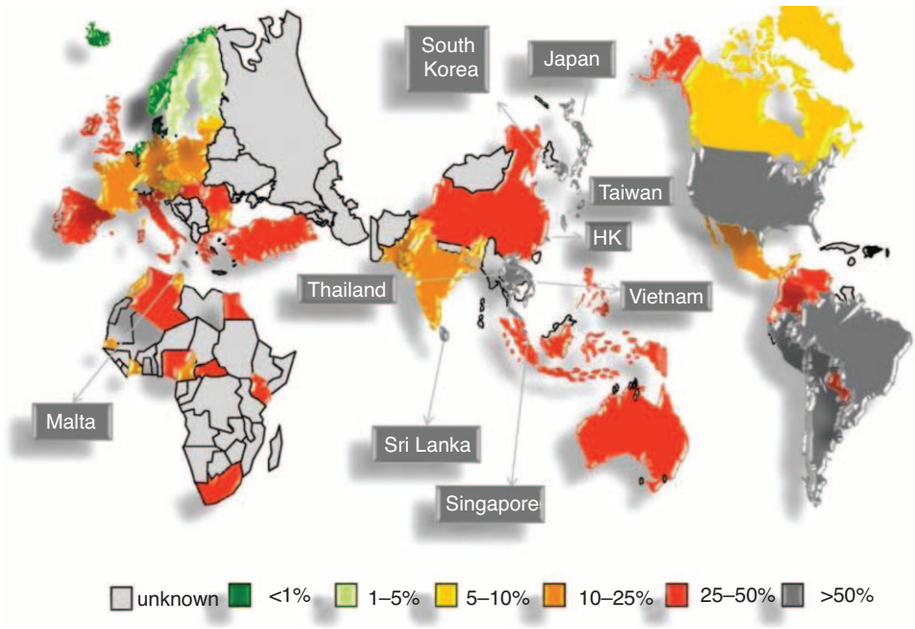

Fig. 6. Worldwide prevalence of methicillin-resistant *Staphylococcus aureus* [42–44]. HK, Hong Kong.

Asia. Intermediate rates (25–50%) are observed in China, Australia, Africa and some European countries, including Portugal (49%), Greece (40%), Italy (37%) and Romania (34%). The lowest prevalence was reported in the Netherlands and Scandinavia [42–44]. Very high prevalence of MRSA was reported from Sri Lanka (86.5%), South Korea (77.6%), Vietnam (74.1%), Taiwan (65.0%), Thailand (57.0%) and Hong Kong (56.8%). A lower frequency is found in India (22.6%) [44]. Figure 6 displays the worldwide prevalence of MRSA.

Risk factors

At-risk populations for MRSA include those with HIV, lupus erythematosus, cancer, diabetes and those undergoing transplantation [45]. MRSA is a serious risk to hospitalized patients [46]. People in contact with livestock animals are also at risk for MRSA infections. In 2011, 24.4% of meat and poultry sold in the United States was contaminated with MRSA [47]. Athletes are another group at risk for MRSA associated particularly with fitness centres in the United States.

Treatment

MRSA are resistant to β-lactam antibiotics. The resistance to antibiotics in community-acquired MRSA (CA-MRSA) and hospital-acquired MRSA (HA-MRSA) is different. CA-MRSA are more susceptible to cotrimoxazole, tetracycline and clindamycin, but the choice for treatment of CA-MRSA is vancomycin. HA-MRSA are susceptible to vancomycin [48] as well as some newer antibiotics such as linezolid and daptomycin; both were found to be effective against HA-MRSA and CA-MRSA. Currently, teicoplanin, vancomycin antibiotics are the preferred choices for treatment of MRSA. Unfortunately, new strains of MRSA have appeared that are resistant to vancomycin, known as vancomycin-resistant *S. aureus* [49]. Linezolid, daptomycin and tigecycline are used for treatment of infections by vancomycin-resistant *S. aureus* [50].

Acknowledgements

Conflicts of interest

There is no conflict of interest.

References

1. Ryan KJ, Ray CG. *Sherris medical microbiology* (4th ed.). New York: McGraw Hill; 2004.
2. Corbella X, Dominguez MA, Pujol M, Ayats J, Sendra M, R Ariza Pallares J, Gudiol F. **Staphylococcus aureus nasal carriage as a marker for subsequent Staphylococcal infections in intensive care unit patients.** *Eur J Clin Microbiol Infect Dis* 1997; **16**:351–357.
3. Wertheim HF, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA, Nouwen JL. **The role of nasal carriage in Staphylococcus aureus infections.** *Lancet Infect Dis* 2005; **5**:751–762.
4. Berman DS, Schaefler S, Simberkoff MS, Rahal JJ. **Staphylococcus aureus colonization in intravenous drug abusers, dialysis patients, and diabetics.** *J Infect Dis* 1987; **155**:829–831.
5. Nguyen MH, Kauffman CA, Goodman RP, Squier C, Arbeit RD, Singh N, *et al*. **Nasal carriage of and infection with Staphylococcus aureus in HIV-infected patients.** *Ann Intern Med* 1999; **130**:221–225.
6. Kluytmans J, van Belkum A, Verbrugh H. **Nasal carriage of Staphylococcus aureus: epidemiology, underlying mechanisms, and associated risks.** *Clin Microbiol Rev* 1997; **10**:505–520.
7. Armstrong-Esther CA. **Carriage patterns of Staphylococcus aureus in a healthy non-hospital population of adults and children.** *Ann Hum Biol* 1976; **3**:221–227.

8. Eriksen NH, Espersen F, Rosdahl VT, Jensen K. **Carriage of Staphylococcus aureus among 104 healthy persons during a 19-month period.** *Epidemiol Infect* 1995; **115**:51–60.
9. Cespedes C, Said-Salim B, Miller M, Lo SH, Kreiswirth BN, Gordon RJ, *et al*. **The clonality of Staphylococcus aureus nasal carriage.** *J Infect Dis* 2005; **191**:444–452.
10. Lina G, Piemont Y, Godail-Gamot F, Bes M, Peter MO, Gauduchon V, *et al*. **Involvement of panton-valentine leukocidin-producing Staphylococcus aureus in primary skin infections and pneumonia.** *Clin Infect Dis* 1999; **29**:1128–1132.
11. Diekema DJ, Pfaller MA, Schmitz FJ, Smayevsky J, Bell J, Jones RN, Beach M. **Survey of infections due to Staphylococcus species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific Region for the Sentry Antimicrobial Surveillance Program, 1997–1999.** *Clin Infect Dis* 2001; **32 (Suppl 2)**:S114–S132.
12. Eggimann P, Pittet D. **Overview of catheter-related infections with special emphasis on prevention based on educational programs.** *Clin Microbiol Infect* 2002; **8**:295–309.
13. Dinges MM, Orwin PM, Schlievert PM. **Exotoxins of Staphylococcus aureus.** *Clin Microbiol Rev* 2000; **13**:16–34; table of contents.
14. Demerec M. **Production of Staphylococcus strains resistant to various concentrations of penicillin.** *Proc Natl Acad Sci U S A* 1945; **31**:16–24.
15. Murray BE, Moellering RC Jr. **Patterns and mechanisms of antibiotic resistance.** *Med Clin North Am* 1978; **62**:899–923.
16. Jevons MP, Parker MT. **The evolution of new hospital strains of Staphylococcus aureus.** *J Clin Pathol* 1964; **17**:243–250.
17. Jevons M. **'Celbenin' – resistant Staphylococci.** *BMJ* 1961; **1**:124–125.
18. Grubb WB. **Genetics of MRSA.** *Rev Med Microbiol* 1998; **9**:153–162.
19. Delaney JA, Schneider-Lindner V, Brassard P, Suissa S. **Mortality after infection with methicillin-resistant Staphylococcus aureus (Mrsa) diagnosed in the community.** *BMC Med* 2008; **6**:2.
20. Grundmann H, Aires-de-Sousa M, Boyce J, Tiemersma E. **Emergence and resurgence of methicillin-resistant Staphylococcus aureus as a public health threat.** *Lancet* 2006; **368**:874–885.
21. Navarre WW, Schneewind O. **Surface proteins of Gram-positive bacteria and mechanisms of their targeting to the cell wall envelope.** *Microbiol Mol Biol Rev* 1999; **63**:174–229.
22. Giesbrecht P, Kersten T, Maidhof H, Wecke J. **Staphylococcal cell wall: morphogenesis and fatal variations in the presence of penicillin.** *Microbiol Mol Biol Rev* 1998; **62**:1371–1414.
23. Wu SW, de Lencastre H, Tomasz A. **Recruitment of the Meca gene homologue of Staphylococcus sciuri into a resistance determinant and expression of the resistant phenotype in Staphylococcus aureus.** *J Bacteriol* 2001; **183**:2417–2424.
24. Katayama Y, Ito T, Hiramatsu K. **A new class of genetic element, Staphylococcus cassette chromosome Mec, encodes methicillin resistance in Staphylococcus aureus.** *Antimicrob Agents Chemother* 2000; **44**:1549–1555.
25. Ito T, Katayama Y, Hiramatsu K. **Cloning and nucleotide sequence determination of the entire Mec DNA of pre-methicillin-resistant Staphylococcus aureus N315.** *Antimicrob Agents Chemother* 1999; **43**:1449–1458.
26. Lowy FD. **Antimicrobial resistance: the example of Staphylococcus aureus.** *J Clin Invest* 2003; **111**:1265–1273.
27. Jensen SO, Lyon BR. **Genetics of antimicrobial resistance in Staphylococcus aureus.** *Future Microbiol* 2009; **4**:565–582.
28. Berger-Bachi B. **Genetic basis of methicillin resistance in Staphylococcus aureus.** *Cell Mol Life Sci* 1999; **56**:764–770.
29. Kuo SC, Chiang MC, Lee WS, Chen LY, Wu HS, Yu KW, *et al*. **Comparison of microbiological and clinical characteristics based on Sccmec typing in patients with community-onset meticillin-resistant Staphylococcus aureus (Mrsa) bacteraemia.** *Int J Antimicrob Agents* 2012; **39**:22–26.
30. Ito T, Ma XX, Takeuchi F, Okuma K, Yuzawa H, Hiramatsu K. **Novel type V Staphylococcal cassette chromosome Mec driven by a novel cassette chromosome recombinase, Ccrc.** *Antimicrob Agents Chemother* 2004; **48**:2637–2651.
31. Hiramatsu K, Cui L, Kuroda M, Ito T. **The emergence and evolution of methicillin-resistant Staphylococcus aureus.** *Trends Microbiol* 2001; **9**:486–493.
32. Boyle-Vavra S, Ereshefsky B, Wang CC, Daum RS. **Successful multiresistant community-associated methicillin-resistant Staphylococcus aureus lineage from Taipei, Taiwan, that carries either the novel Staphylococcal chromosome cassette Mec (Sccmec) Type Vt or Sccmec Type Iv.** *J Clin Microbiol* 2005; **43**:4719–4730.
33. Klevens RM, Edwards JR, Tenover FC, McDonald LC, Horan T, Gaynes R. **Changes in the epidemiology of methicillin-resistant Staphylococcus aureus in intensive care units in US hospitals, 1992–2003.** *Clin Infect Dis* 2006; **42**:389–391.
34. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. **The impact of methicillin resistance in Staphylococcus aureus bacteremia on patient outcomes: mortality, length of stay, and hospital charges.** *Infect Control Hosp Epidemiol* 2005; **26**:166–174.
35. 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.
36. Aires de Sousa M, Conceicao T, Simas C, de Lencastre H. **Comparison of genetic backgrounds of methicillin-resistant and -susceptible Staphylococcus aureus isolates from Portuguese hospitals and the community.** *J Clin Microbiol* 2005; **43**:5150–5157.
37. Zinn CS, Westh H, Rosdahl VT. **The Sarisa Study Group: an international multicenter study of antimicrobial resistance and typing of hospital Staphylococcus aureus isolates from 21 laboratories in 19 countries or states.** *Microb Drug Resist* 2004; **10**:160–168.
38. Rohani M. **Antibiotic resistance patterns of bacteria isolated in Malaysian hospitals.** *Int Med J* 1999; **6**:47–51.
39. Tiemersma EW, Bronzwaer SL, Lyytikainen O, Degener JE, Schrijnemakers P, Bruinsma N, *et al*., European Antimicrobial Resistance Surveillance System Participants. **Methicillin-resistant Staphylococcus aureus in Europe, 1999–2002.** *Emerg Infect Dis* 2004; **10**:1627–1634.
40. Musa HA, Shears P, Khagali A. **First report of MRSA from hospitalized patients in sudan.** *J Hosp Infect* 1999; **42**:74.
41. Centers for Disease Control and Prevention. *MRSA surveillance*. Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.
42. Grundmann H, Aanensen DM, van den Wijngaard CC, Spratt BG, Harmsen D, Friedrich AW. **Geographic distribution of Staphylococcus aureus causing invasive infections in Europe: a molecular-epidemiological analysis.** *PLoS Med* 2010; **7**:e1000215.
43. Mejia C, Zurita J, Guzman-Blanco M. **Epidemiology and surveillance of methicillin-resistant Staphylococcus aureus in Latin America.** *Braz J Infect Dis* 2010; **14 (Suppl 2)**:S79.
44. Song JH, Hsueh PR, Chung DR, Ko KS, Kang CL, Peck KR. **Spread of methicillin-resistant Staphylococcus aureus between the community and the hospitals in Asian countries: an ANSORP study.** *J Antimicrob Chemother* 2011; **66**:1061–1069.
45. Lipsky BA, Tabak YP, Johannes RS, Vo L, Hyde L, Weigelt JA. **Skin and soft tissue infections in hospitalised patients with diabetes: culture isolates and risk factors associated with mortality, length of stay and cost.** *Diabetologia* 2010; **53**:914–923.
46. Kazakova SV, Hageman JC, Matava M, Srinivasan A, Phelan L, Garfinkel B, *et al*. **A clone of methicillin-resistant Staphylococcus aureus among professional football players.** *N Engl J Med* 2005; **352**:468–475.
47. Ogata K, Narimatsu H, Suzuki M, Higuchi W, Yamamoto T, Taniguchi H. **Commercially distributed meat as a potential vehicle for community-acquired methicillin-resistant Staphylococcus aureus.** *Appl Environ Microbiol* 2012; **78**:2797–2802.
48. Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. **Linezolid Vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant Staphylococcus aureus nosocomial pneumonia.** *Chest* 2003; **124**:1789–1797.
49. Centers for Disease Control and Prevention. **Vancomycin-resistant Staphylococcus aureus – Pennsylvania, 2002.** *MMWR Morb Mortal Wkly Rep* 2002; **51**:902.
50. Mongkolrattanothai K, Boyle S, Kahana MD, Daum RS. **Severe Staphylococcus aureus infections caused by clonally related community-associated methicillin-susceptible and methicillin-resistant isolates.** *Clin Infect Dis* 2003; **37**:1050–1058.