Original Article

Molecular Epidemiology of *Staphylococcus aureus* among Patients with Skin and Soft Tissue Infections in Two Chinese Hospitals

Fei-Fei Gu[1], Ye Chen[2], De-Ping Dong[2], Zhen Song[3], Xiao-Kui Guo[4], Yu-Xing Ni[1], Li-Zhong Han[1]

[1]Department of Clinical Microbiology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China
[2]Laboratory, Haian Hospital, Nantong University, Nantong, Jiangsu 226600, China
[3]Faculty of Laboratory Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China
[4]Department of Microbiology and Parasitology, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

Fei-Fei Gu and Ye Chen contributed equally to this work.

Abstract

Background: *Staphylococcus aureus* is one of the predominant causes of skin and soft tissue infections (SSTIs), but limited data were available regarding the characterization of *S. aureus* from SSTIs patients in Jiangsu Province in China. We aimed to investigate the molecular epidemiology of *S. aureus* among SSTIs patients in two hospitals of Jiangsu Province.
Methods: Sixty-two patients with SSTIs from two Chinese hospitals in Jiangsu Province were enrolled in this study, and 62 *S. aureus* isolates were collected from February 2014 to January 2015. *S. aureus* isolates were characterized by antimicrobial susceptibility testing, toxin gene detection, and molecular typing with sequence type, Staphylococcus protein A gene type, accessory gene regulator (*agr*) group, and Staphylococcal cassette chromosome *mec* type.
Results: Sixteen (25.8%) methicillin-resistant *S. aureus* (MRSA) isolates were detected, and there was no isolate found resistant to vancomycin, teicoplanin, sulfamethoxazole-trimethoprim, and linezolid. The *sei* was the toxin gene most frequently found, and no *lukS/F-PV*-positive isolates were detected among the SSTIs' patients. Molecular analysis revealed that ST398 (10/62, 16.1%; 2 MRSA and 8 methicillin-susceptible *S. aureus*) to be the dominant clone, followed by ST5 (8/62, 12.9%) and ST7 (8/62, 12.9%).
Conclusions: The livestock ST398 was the most common clone among patients with *S. aureus* SSTIs in Jiangsu Province, China. Surveillance and further studies on the important livestock ST398 clone in human infections are necessarily requested.

Key words: Livestock; Molecular Epidemiology; Skin and Soft Tissue Infections; ST398; *Staphylococcus aureus*

Introduction

Skin and soft tissue infections (SSTIs) range from relatively common superficial skin infections to rare but life-threatening infections such as necrotizing fasciitis or gas gangrene.[1] *Staphylococcus aureus* is the most common pathogen in SSTIs across all continents, causing a variety of SSTIs ranging from the benign (e.g., impetigo and uncomplicated cellulitis) to the immediately life-threatening.[2] While *S. aureus* has traditionally been the leading cause of SSTIs, its importance has ballooned in the past 15 years with the emergence of a worldwide epidemic of community-associated methicillin-resistant *S. aureus* (MRSA) SSTIs.[3] The developing resistance to antibiotics and the presence of virulence factors playing roles in SSTIs such as Panton-Valentine leukocidin (PVL) and toxic shock syndrome toxin (TSST) lead to major challenges in preventing and treating patients with *S. aureus* SSTIs.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.190673

Address for correspondence: Dr. Li-Zhong Han, Department of Clinical Microbiology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China
E-Mail: hanlizhong1107@163.com

Received: 27-05-2016 **Edited by:** Qiang Shi
How to cite this article: Gu FF, Chen Y, Dong DP, Song Z, Guo XK, Ni YX, Han LZ. Molecular Epidemiology of *Staphylococcus aureus* among Patients with Skin and Soft Tissue Infections in Two Chinese Hospitals. Chin Med J 2016;129:2319-24.

In China, CC59 was the dominant clonal complex among *S. aureus*, especially MRSA among the patients with SSTIs, and ST7 has become the common clone recently in methicillin-susceptible *S. aureus* (MSSA) SSTIs.[4,5] The livestock-associated clone ST398, which was always associated with animals and farm workers,[6] was currently found frequently with a high positive rate of *lukS/F-PV* among *S. aureus* in SSTIs patients in China.[4,7] CC8 was the most common clone among SSTIs-associated *S. aureus*, especially MRSA in the United States and Japan.[8,9] Moreover, the prevalence of *S. aureus* colonization among SSTIs patients was high in the United States and USA300 (CC8) MRSA was often involved as reported.[10]

Jiangsu Province lies in the east of China and is adjacent to Shanghai. The livestock husbandry of the two cities enrolled in this study in Jiangsu Province was well developed. To the best of our knowledge, there were no published data regarding the molecular epidemiology of *S. aureus* among patients with SSTIs in Jiangsu Province in China. Thus, the aim of the current study was to investigate the genetic diversity of *S. aureus* from SSTIs patients in two Chinese hospitals in Jiangsu Province, China.

Methods

Study design and setting

A total of 62 patients with SSTIs from two Chinese hospitals in two cities (Affiliated Hospital of Nantong University and Jiangsu Taizhou People's Hospital, 41 and 21 patients, respectively) of Jiangsu Province were enrolled in this study, and 62 *S. aureus* isolates were collected during February 2014 to January 2015. The experiments in this study were performed in Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai.

This study was approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, and the Review Board exempted the need for informed consent for this retrospective study mainly focused on bacteria without interventions involving patients.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed according to the guidelines of Clinical and Laboratory Standards Institute.[11] Antibiotics including penicillin (10 units), cefoxitin (30 μg), gentamicin (10 μg), kanamycin (30 μg), tobramycin (10 μg), erythromycin (15 μg), tetracycline (30 μg), teicoplanin (30 μg), minocycline (30 μg), ciprofloxacin (5 μg), clindamycin (2 μg), sulfamethoxazole-trimethoprim (25 μg), chloramphenicol (30 μg), rifampicin (5 μg), quinupristin-dalfopristin (15 μg), linezolid (30 μg), fusidic acid (10 μg), and mupirocin (5 μg and 200 μg) were tested by the disk diffusion method, and all the disks were Oxoid paper disks (Oxoid, UK). The minimum inhibitory concentration of vancomycin was detected by E-test (bioMerieux, France). The penicillin disk diffusion zone edge test was performed for β-lactamase detection, and inducible clindamycin resistance was determined by the D-test. *S. aureus* ATCC25923 and ATCC29213 were used as quality controls for the disk diffusion test and E-test, respectively.

Detection of toxin genes

A variety of clinically significant toxin genes were detected by polymerase chain reaction,[12] including *lukS/F-PV* (encoding Panton-Valentine leukocidin); *tst* (encoding toxic shock syndrome toxin 1); *eta* and *etb* (encoding exfoliative toxin A and B); *sea-see* and *seg-sej* (encoding staphylococcal enterotoxins SEA-SEE and SEG-SEJ); and *sasX* (encoded in a mobile genetic element), which act as a virulence determinant and play a key role in MRSA colonization and pathogenesis.

Molecular typing

Molecular typing including multilocus sequence typing (MLST) and Staphylococcus protein A gene (*spa*) typing was performed on all *S. aureus*.[13] For confirming the presence of MRSA, *mecA* detection was performed on all *S. aureus* collected. Staphylococcal cassette chromosome *mec* (SCC*mec*) types of MRSA were determined by the method described previously.[14]

Statistical analysis

The Chi-square or Fisher's exact test was used where appropriate using the SPSS software package (SPSS19.0, IBM-SPSS Inc, Armonk, NY, USA). A two-sided $P < 0.05$ was considered statistically significant.

Results

Clinical data

The median age of patients with SSTIs in this study was 50 years (range: 6 months to 95 years), and the gender distribution (male/female) was 40/22 (64.5%/35.5%). Forty of 62 patients were considered outpatients, and the rest 20 patients were inpatients. In terms of the infection types, abscesses (69.4%) was the most common infection type. Clinical data on any possible patient contact with animals were lack in this study.

Antimicrobial susceptibility testing

Sixteen (25.8%) isolates were confirmed as MRSA in this study. We did not find any isolated resistant to vancomycin, teicoplanin, sulfamethoxazole-trimethoprim, and linezolid. The resistance rates of other antibiotics tested are shown in Table 1. A total of 35 isolates (27 MSSA and 8 MRSA) were inducible resistance to clindamycin based on D-test results. One MRSA isolate (ST5-SCC*mec*I-t311) was observed showing high-level mupirocin resistance.

Virulence factors

The toxin genes *lukS/F-PV*, *etb*, *see*, and *sasX* were not detected among all *S. aureus* isolates in this study. The *sei* was most frequently found among the toxin genes we screened for, occurring in 16 isolates (25.8%) as shown in Table 2. The *tst* was found in 3 isolates (1 MSSA and 2 MRSA) and all the 3 isolates were belonging to ST5. There

was no significant difference observed in prevalence of the toxin genes between the MSSA and MRSA groups.

Molecular types

ST398 was the most common clone which detected in 10 isolates (2 MRSA and 8 MSSA) accounting for 16.1% among SSTIs patients. Both ST5 and ST7 were the second common clones (both 8/62, 12.9%), and 4 ST5 MRSA isolates and 1 ST7 MRSA isolate were identified as shown in Table 3. The relationships of *S. aureus* isolates are shown in a rough sketch produced by eBURST based on the MLST data of this study [Figure 1]. The *spa* type was identified in 38 types and it expressed a great diversity in this study. There was not an outstanding *spa* type that found in more than 5 isolates, and t4549 and t571 were the most common *spa* type relatively which were both detected in 4 isolates (6.5%). In total, we detected 5 SCC*mec* Type I, 3 SCC*mec* Type II, and 8 SCC*mec* Type V isolates. The *agrI* (32/62, 51.6%) was the most frequent *agr* group, followed by *agrII* (21/62, 33.9%), *agrIII* (5/62, 8.1%), and *agrIV* (4/62, 6.4%).

Discussion

In this study, 16 MRSA isolates were detected accounting for 25.8%, and it was higher than the occurrence of MRSA among *S. aureus* from SSTIs as we studied in Shanghai previously.[4] However, it was lower than the occurrence of MRSA among *S. aureus* SSTIs as reported in Canada.[15] Considering the importance of MRSA in SSTIs and its involvement associated with poor patient outcomes, vancomycin, teicoplanin, linezolid, daptomycin, tigecycline, and ceftaroline were recommended by European guidelines for the treatment of MRSA complicated SSTIs (cSSTIs).[16] According to the study which conducted more than 10 years in Europe, clinical efficacy and favorable outcomes of linezolid have been demonstrated for the treatment of MRSA cSSTIs, including the treatment of lower extremity infections.[16]

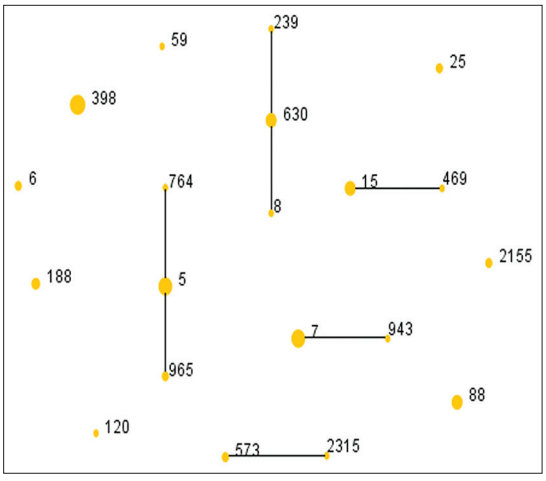

Figure 1: The diagram produced by eBURST with the stringent (default) group definition. Each number represents an MLST ST and the area of each circle indicates the prevalence of the ST in the MLST data of this study. MLST: Multilocus sequence typing; ST: Sequence type.

ST398 was found to be the most common clone within all the *S. aureus* isolates studied. ST398 was a livestock-associated clone and has been reported as a common but not the most common clone among patients with *S. aureus* SSTIs in

Table 1: The antibiotic resistance rates of *Staphylococcus aureus* isolated from patients with skin and soft tissue infections in two Chinese hospitals

Antibiotics	Resistance rate (%)		
	Total (n = 62)	MSSA (n = 46)	MRSA (n = 16)
Penicillin	90.3	87.0	100
Gentamicin	12.9	4.3	37.5
Kanamycin	22.6	8.7	62.5
Tobramycin	17.7	10.9	37.5
Erythromycin	69.4	65.2	81.3
Tetracycline	22.6	15.2	43.8
Minocycline	1.6	0	6.3
Ciprofloxacin	14.5	8.7	31.3
Clindamycin*	14.5	8.7	31.3
Chloramphenicol	4.8	4.3	6.3
Rifampicin	1.6	0	6.3
Quinupristin-dalfopristin	1.6	0	6.3
Fusidic acid	4.8	0	6.3
Mupirocin†	1.6	0	6.3

*35 isolates (27 MSSA and 8 MRSA) were *D*-test positive, indicating inducible clindamycin resistance; †One MRSA isolate presented high-level mupirocin resistance. MSSA: Methicillin-susceptible *Staphylococcus aureus*; MRSA: Methicillin-resistant *Staphylococcus aureus*.

Table 2: Prevalence of toxin genes among *Staphylococcus aureus* isolated from patients with skin and soft tissue infections in two Chinese hospitals

Toxin genes	Positive rate (%)			χ^2	P
	Total (n = 62)	MSSA (n = 46)	MRSA (n = 16)		
lukS/F-PV	0	0	0	–	–
tst	4.8	2.2	12.5	0.964	0.326
eta	3.2	4.3	0	0.001	0.979
etb	0	0	0	–	–
sea	8.1	4.3	18.8	1.663	0.197
seb	4.8	4.3	6.3	<0.001	1.000
sec	19.4	13.0	37.5	0.873	0.350
sed	8.1	8.7	6.3	<0.001	1.000
see	0	0	0	–	–
seg	12.9	10.9	18.8	0.142	0.706
seh	3.2	2.2	6.3	–	0.453
sei	25.8	23.9	31.3	0.061	0.806
sej	6.5	6.5	6.3	<0.001	1.000
sasX	0	0	0	–	–

lukS/F-PV: Gene encoding Panton-Valentine leukocidin; *tst*: Gene encoding toxic shock syndrome toxin 1; *eta* and *etb*: Gene encoding exfoliative toxin A and B; *sea-see* and *seg-sej*: Gene encoding staphylococcal enterotoxins SEA-SEE and SEG-SEJ; *sasX*: Gene encoding mobile genetic element; Two-sided P value calculated by the Chi-square or Fisher's exact test as appropriate. –: Not applicable; MSSA: Methicillin-susceptible *Staphylococcus aureus*; MRSA: Methicillin-resistant *Staphylococcus aureus*.

Table 3: Molecular characteristics of *Staphylococcus aureus* isolated from patients with skin and soft tissue infections in two Chinese hospitals

CC	ST	Isolates, *n*	SCC*mec* type	*spa* type (*n*)	Virulence factors (*n*)
1	573	2		t8915 (1), t4938 (1)	*sec* (1), *sei* (1)
	2315	1		t11687 (1)	*sec* (1), *seg* (1), *sei* (1)
5	5	8	I	t311 (1), t2460 (1)	*tst* (1), *sec* (1), *seg* (2), *sei* (2)
			II	t311 (2)	*tst* (1), *sea* (2), *sec* (1), *seg* (1), *sei* (2)
				t954 (2), t548 (1), t5734 (1)	*tst* (1), *sed* (3), *seg* (2), *sei* (4), sej (2)
	965	2	I	t15075 (1)	*sed* (1), *sei* (1), *sej* (1)
				t062 (1)	*sea* (1), *seg* (1), *sei* (1)
	764	1	II	t002 (1)	None
6	6	2		t701 (2)	*eta* (1), *sea* (1)
7	7	8	V	t796 (1)	None
				t091 (3), t796 (2), t1685 (1), t3714 (1)	*sec* (1)
	943	1		t1867 (1)	*seh* (1)
8	8	1		t9101 (1)	*sed* (1), *sej* (1)
	239	1	V	t030 (1)	sea (1)
	630	4	V	t4549 (4)	None
		1		t5554	None
15	15	5		t084 (3), t085 (1), t14014 (1)	None
	468	1		t774 (1)	None
25	25	2		t078 (2)	*seb* (2), *sei* (2)
59	59	1	I	t437 (1)	*seb* (1), *seh* (1)
88	88	1	I	t15076 (1)	None
		4		t3155 (2), t1376 (1), t15074 (1)	None
121	120	1		t435 (1)	*sei* (1)
	2155	2		t1425 (2)	*eta* (1), *seg* (1), *sei* (1)
188	188	3		t189 (3)	None
398	398	10	V	t034 (1), t1928 (1)	None
				t571 (4), t034 (2), t1451 (2)	None

CC: Clonal complex; ST: Sequence type by multi-locus sequence typing; SCC*mec*: Staphylococcal cassette chromosome *mec*; *spa*: Staphylococcus protein A gene; None: No toxin gene detected.

Shanghai and Beijing, China before.[4,7] It has also been reported unexpectedly high among bone and joint infections and nasal-colonizing isolates in France.[17] The *spa* type t034 which was found among all ST398 *S. aureus* isolates was reported as a dominant type in pigs and pig farmers in Canada.[18] According to the documents in 2014, in the two cities in Jiangsu Province involved in this study, a total of 11.5 million pigs, 5.5 million sheep, and 208.6 million fowls were breed, of which 7.0 million pigs, 3.0 million sheep, and 142.6 million fowls were sold to nearby cities like Shanghai. The livestock husbandry in the two cities is well developed and a great number of people in these two cities are engaged in livestock husbandry or other related works. The high prevalence of ST398 *S. aureus* we observed in this study suggested that ST398 might be related to livestock or farm working. It was the limitation that we lack any clinical data on any possible patient contact with animals. Nevertheless, it was still suggested that CC398 *S. aureus* is mostly disseminated through direct contact to livestock, and a substantial proportion of patients seem to acquire MRSA CC398 through other pathways.[19] Epidemiological and genetic analyses revealed that human MRSA of unknown origin CC398 carriers carried MRSA from livestock origin, suggestive of indirect transmission. Although the exact transmission route remains unknown, direct human-to-human transmission remains a possibility as well.[20] In addition to the region or the transmission of CC398 *S. aureus*, the question how CC398 *S. aureus* could become the predominant clone in human infections so fast in China even in other countries during these years should be a matter of concern that need further studies.

Both ST5 and ST7 were the second common clones in this study. ST5 was a pandemic HA-MRSA clone disseminated internationally in Asia.[21] It was noteworthy that the toxin gene *tst* encoding TSST-1 was found in 3 isolates and all the 3 isolates were belonging to ST5. Moreover, the TSST-1 ST5 has been described in China and France before.[22,23] Besides frequently discovered among SSTIs patients in China currently, ST7 was also found to be the most common genotype of MSSA in invasive community-acquired *S. aureus* infection in Chinese children.[24]

CC8 (ST8, ST239, and ST630) was totally observed in 7 isolates as shown in Table 3. ST8 (USA300) has led to a high burden of SSTIs globally ever since its emergence in 2000 in the United States, as witnessed by *S. aureus* clone outbreak among SSTIs in many countries;[4] however, we only found one ST8 MSSA in SSTIs patients in this study. ST239 is recognized as a common epidemic clone in bloodstream infections[13] and ST630 was recently reported to cause severe infective endocarditis with systemic embolism in China.[25]

CC59 which is always the most clonal complex among patients with SSTIs in China was found only in one MRSA isolate. PVL production by *S. aureus* may play a key role in the pathogenesis of *S. aureus* SSTIs.[26] However, we have not detected any *lukS/F-PV*-positive isolate among patients with SSTIs in this study.

In conclusion, ST398 was the most common clone among patients with *S. aureus* SSTIs in Jiangsu Province, China. The livestock ST398 might be the predominant clone in *S. aureus*, causing SSTIs in the region where livestock is well developed. Surveillance and further studies on the important livestock ST398 clone in human infections are necessarily requested.

Acknowledgment

We thank Shao-Peng Chu (Laboratory, Affiliated Hospital of Nantong University, Nantong, Jiangsu Province) and Qing-Fang Zhang (Laboratory, Jiangsu Taizhou People's Hospital, Taizhou, Jiangsu Province) for their kind help and cooperation in collecting isolates.

Financial support and sponsorship

This work was supported by a grant from the National Natural Science Foundation of China (No. 81472010).

Conflicts of interest

There are no conflicts of interest.

References

1. Török ME, Conlon CP. Skin and soft tissue infections. Medicine 2013;41:709-15. doi: 10.1016/j.mpmed.2013.10.001.
2. Cardona AF, Wilson SE. Skin and soft-tissue infections: A critical review and the role of telavancin in their treatment. Clin Infect Dis 2015;61 Suppl 2:S69-78. doi: 10.1093/cid/civ528.
3. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. *Staphylococcus aureus* infections: Epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev 2015;28:603-61. doi: 10.1128/CMR.00134-14.
4. Gu FF, Hou Q, Yang HH, Zhu YQ, Guo XK, Ni YX, *et al.* Characterization of *Staphylococcus aureus* isolated from non-native patients with skin and soft tissue infections in Shanghai. PLoS One 2015;10:e0123557. doi: 10.1371/journal.pone.0123557.
5. Yu F, Liu Y, Lv J, Qi X, Lu C, Ding Y, *et al.* Antimicrobial susceptibility, virulence determinant carriage and molecular characteristics of *Staphylococcus aureus* isolates associated with skin and soft tissue infections. Braz J Infect Dis 2015;19:614-22. doi: 10.1016/j.bjid.2015.08.006.
6. Vandendriessche S, Vanderhaeghen W, Larsen J, de Mendonça R, Hallin M, Butaye P, *et al.* High genetic diversity of methicillin-susceptible *Staphylococcus aureus* (MSSA) from humans and animals on livestock farms and presence of SCCmec remnant DNA in MSSA CC398. J Antimicrob Chemother 2014;69:355-62. doi: 10.1093/jac/dkt366.
7. Zhao C, Liu Y, Zhao M, Liu Y, Yu Y, Chen H, *et al*. Characterization of community acquired *Staphylococcus aureus* associated with skin and soft tissue infection in Beijing: High prevalence of PVL ST398. PLoS One 2012;7:e38577. doi: 10.1371/journal.pone.0038577.
8. Kaltsas A, Guh A, Mediavilla JR, Varshney AK, Robiou N, Gialanellia P, *et al.* Frequency of panton-valentine leukocidin-producing methicillin-sensitive *Staphylococcus strains* in patients with complicated skin and soft tissue infection in bronx, new york. J Clin Microbiol 2011;49:2992-5. doi: 10.1128/JCM.00704-11.
9. Maeda T, Saga T, Miyazaki T, Kouyama Y, Harada S, Iwata M, *et al.* Genotyping of skin and soft tissue infection (SSTI)-associated methicillin-resistant *Staphylococcus aureus* (MRSA) strains among outpatients in a teaching hospital in Japan: Application of a phage-open reading frame typing (POT) kit. J Infect Chemother 2012;18:906-14. doi: 10.1007/s10156-012-0506-4.
10. Kumar N, David MZ, Boyle-Vavra S, Sieth J, Daum RS. High *Staphylococcus aureus* colonization prevalence among patients with skin and soft tissue infections and controls in an urban emergency department. J Clin Microbiol 2015;53:810-5. doi: 10.1128/JCM.03221-14.
11. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement. CLSI Document M100-S24. Vol. 34. Wayne, PA, USA: Clinical and Laboratory Standards Institute; 2014.
12. Gu FF, Han LZ, Chen X, Wang YC, Shen H, Wang JQ, *et al.* Molecular characterization of *Staphylococcus aureus* from surgical site infections in orthopedic patients in an orthopedic trauma clinical medical center in Shanghai. Surg Infect (Larchmt) 2015;16:97-104. doi: 10.1089/sur.2014.027.
13. Chen X, Wang WK, Han LZ, Liu Y, Zhang H, Tang J, *et al.* Epidemiological and genetic diversity of *Staphylococcus aureus* causing bloodstream infection in Shanghai, 2009-2011. PLoS One 2013;8:e72811. doi: 10.1371/journal.pone.0072811.
14. Chen X, Yang HH, Huangfu YC, Wang WK, Liu Y, Ni YX, *et al.* Molecular epidemiologic analysis of *Staphylococcus aureus* isolated from four burn centers. Burns 2012;38:738-42. doi: 10.1016/j.burns.271.12.023.
15. Borgundvaag B, Ng W, Rowe B, Katz K; EMERGency Department Emerging Infectious Disease Surveillance NeTwork (EMERGENT) Working Group. Prevalence of methicillin-resistant *Staphylococcus aureus* in skin and soft tissue infections in patients presenting to Canadian emergency departments. CJEM 2013;15:141-60. doi: 10.2310/8000.2013.130798.
16. Bassetti M, Baguneid M, Bouza E, Dryden M, Nathwani D, Wilcox M. European perspective and update on the management of complicated skin and soft tissue infections due to methicillin-resistant *Staphylococcus aureus* after more than 10 years of experience with linezolid. Clin Microbiol Infect 2014;20 Suppl 4:3-18. doi: 10.1111/1469-0691.12463.
17. Valour F, Tasse J, Trouillet-Assant S, Rasigade JP, Lamy B, Chanard E, *et al.* Methicillin-susceptible *Staphylococcus aureus* clonal complex 398: High prevalence and geographical heterogeneity in bone and joint infection and nasal carriage. Clin Microbiol Infect 2014;20:O772-5. doi: 10.1111/1469-0691.12567.
18. Khanna T, Friendship R, Dewey C, Weese JS. Methicillin resistant *Staphylococcus aureus* colonization in pigs and pig farmers. Vet Microbiol 2008;128:298-303. doi: 10.1016/j.vetmic.2007.10.006.
19. Deiters C, Günnewig V, Friedrich AW, Mellmann A, Köck R. Are cases of Methicillin-resistant *Staphylococcus aureus* clonal complex (CC) 398 among humans still livestock-associated? Int J Med Microbiol 2015;305:110-3. doi: 10.1016/j.ijmm.2014.11.007.
20. Lekkerkerk WS, van Wamel WJ, Snijders SV, Willems RJ, van Duijkeren E, Broens EM, *et al.* What is the origin of livestock-associated methicillin-resistant *Staphylococcus aureus* clonal complex 398 isolates from humans without livestock contact? An epidemiological and genetic analysis. J Clin Microbiol 2015;53:1836-41. doi: 10.1128/JCM.02702-14.
21. Chen CJ, Huang YC. New epidemiology of *Staphylococcus aureus* infection in Asia. Clin Microbiol Infect 2014;20:605-23. doi: 10.1111/1469-0691.12705.
22. Zhang J, Gu FF, Zhao SY, Xiao SZ, Wang YC, Guo XK, *et al.* Prevalence and molecular epidemiology of *Staphylococcus aureus* among residents of seven nursing homes in Shanghai. PLoS One 2015;10:e0137593. doi: 10.1371/journal.pone.0137593.
23. Robert J, Tristan A, Cavalié L, Decousser JW, Bes M, Etienne J, *et al.* Panton-valentine leukocidin-positive and toxic shock syndrome toxin 1-positive methicillin-resistant *Staphylococcus aureus*: A French

multicenter prospective study in 2008. Antimicrob Agents Chemother 2011;55:1734-9. doi: 10.1128/AAC.01221-10.
24. Qiao Y, Ning X, Chen Q, Zhao R, Song W, Zheng Y, *et al*. Clinical and molecular characteristics of invasive community-acquired *Staphylococcus aureus* infections in Chinese children. BMC Infect Dis 2014;14:582. doi: 10.1186/s12879-014-0582-4.
25. Zheng B, Jiang S, Xu Z, Xiao Y, Li L. Severe infective endocarditis with systemic embolism due to community associated methicillin-resistant *Staphylococcus aureus* ST630. Braz J Infect Dis 2014;19:85-9. doi: 10.1016/j.bjid.2014.07.006.
26. Gould IM. Antibiotics, skin and soft tissue infection and meticillin-resistant *Staphylococcus aureus*: Cause and effect. Int J Antimicrob Agents 2009;34 Suppl 1:S8-11. doi: 10.1016/s0924-8579(09)70542-4.