

The Dissemination of Fusidic Acid Resistance Among *Staphylococcus epidermidis* Clinical Isolates in Wenzhou, China

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Purpose: Fusidic acid (FA), a potent steroidal antibiotic, is used topically to treat skin and soft tissue infections (SSTIs) caused by *Staphylococci*. The aim of this study is to report the prevalence of fusidic acid resistance among *Staphylococcus epidermidis* clinical isolates from a tertiary hospital in Wenzhou, east China.

Methods: The antibiotic susceptibility of *S. epidermidis* isolates was determined by disc diffusion method and agar dilution method. Then, FA-resistant *S. epidermidis* isolates were characterized by multi-locus sequence typing, SCCmec typing and pulsed-field gel electrophoresis.

Results: In the present study, the 55 (7.7%) FA-resistant *S. epidermidis* among 711 *S. epidermidis* clinical isolates were isolated from different parts of 53 patients. Fifty-five FA-resistant *S. epidermidis* isolates with FA MIC values ranged from 4 to 32 µg/mL. Among them, 50 (90.9%) were identified as methicillin-resistant *Staphylococcus epidermidis* (MRSE), in which *mecA* were positive. Meanwhile, the positive rates of *fusB* and *fusC* genes among FA-resistant *S. epidermidis* isolates were 85.5% (47/55) and 7.3% (4/55), respectively. All 55 isolates mentioned above were susceptible to vancomycin. More than 50% of FA-resistant isolates were resistant to non-β-lactam antimicrobials including erythromycin (80.0%, 44/55), clindamycin (65.5%, 36/55), ciprofloxacin (63.6%, 35/55) and sulfamethoxazole (63.6%, 35/55). A total of 14 sequence types (STs) were identified among the 55 FA-resistant *S. epidermidis* isolates, of which, ST2 (24/55, 43.6%) was the most predominant type. And the eBURST analysis showed that CC2, CC5 and CC247 accounted for 43.6% (24/55), 27.3% (15/55) and 14.5% (5/55), respectively. Meanwhile, a total of four SCCmec types (I, III, IV, V) were identified among the 55 FA-resistant *S. epidermidis*. Furthermore, the pulsed field gel electrophoresis divided the 55 isolates into 20 types, namely A-T. Q-type strains were most prevalent, accounting for 30.9% (17/55).

Conclusion: Taken together, the dissemination of *S. epidermidis* ST2 clone with FA resistance can cause trouble in controlling *S. epidermidis* infections.

Keywords: *Staphylococcus epidermidis*, fusidic acid, resistance, molecular characteristics

Introduction

Staphylococcus epidermidis is a member of the coagulase-negative staphylococci (CoNS), considered a component of the normal commensal microflora in human.¹ Colonization by *S. epidermidis* contributes to the maintenance of a healthy skin flora, especially by competing with potentially harmful microorganisms such as *Staphylococcus aureus*.² However, in recent decades, with the increased use of indwelling or implanted medical devices and the increase of sickly, elderly and immunocompromised patients, *S. epidermidis* has emerged as an important opportunistic pathogen responsible for hospital-acquired infections, particularly biofilm-associated infections.³

Fusidic acid, employed for the treatment of superficial and systemic disease caused by *staphylococci*, is a valuable alternative to vancomycin for the infections caused by multi-drug resistant *Staphylococci*, especially the infection of methicillin-resistant *Staphylococcus aureus*.^{4–6} But there is a concern that there is a significant trend towards increased

FA resistance among *Staphylococci* with increased duration of use, which is an even greater problem for limiting our therapeutic options.^{1,7} Fusidic acid inhibits elongation factor G (EF-G) release from ribosomes and eventually blocks the synthesis of bacterial proteins.⁸ As in *S. aureus*, resistance to FA in *S. epidermidis* results either from the mutation of *fusA*, or acquiring *fusB* or *fusC* resistance genes.^{9,10}

Strikingly, studies have shown the proportion of fusidic acid-resistant *S. epidermidis* higher than that in *S. aureus*.^{11,12} Molecular analysis for *S. epidermidis* isolates associated with nosocomial infections has shown considerable clonal diversity and is much less studied than that for *S. aureus*.¹³ Multi-locus sequence typing (MLST) based on nucleotide sequencing of seven housekeeping genes revealed distinct related clones of MRSE from clinically significant isolates and showed a worldwide predominance of only a few hospital-associated, epidemic clonal lineages.¹³ Clonal complex 2 (CC2) was major genetic lineage among the population structure of hospital-acquired *S. epidermidis* worldwide.^{14,15} Limited information of the resistance of *S. epidermidis* clinical isolates to FA is available. The purpose of our study is to investigate the dissemination of FA resistance and molecular characteristics of *S. epidermidis* isolates from hospitalized patients in a tertiary hospital in Wenzhou, east China.

Materials and Methods

Collection of *S. Epidermidis* Clinical Isolates

Seven hundred and seventy-one non-duplicate *S. epidermidis* isolates were collected consecutively from various specimens of inpatients at the first Affiliated Hospital of Wenzhou Medical University. The isolates were identified as *S. epidermidis* by using Gram's stain, catalase test and VITEK automatic microbiology analyzer (bioMe'rieux, Marcy l'Etoile, France).

Screening for Fusidic Acid-Resistant *S. Epidermidis*

The minimum inhibitory concentration (MIC) of FA for *S. epidermidis* isolates was determined by the agar dilution method. The interpretive criterion of FA susceptibility for *Staphylococci* was in accordance with the European Committee for Antimicrobial Susceptibility Testing (EUCAST)/British Society of Antimicrobial Chemotherapy (BSAC) criteria (susceptible, MIC < 2 µg/mL; resistant, MIC ≥ 2 µg/mL).

Antimicrobial Susceptibility Testing

In vitro antimicrobial susceptibility testing was determined by the disk diffusion method with antimicrobials in accordance with the standards recommended by the Clinical and Laboratory Standards Institute (CLSI).¹⁶ Antibiotic discs were tested as follows: penicillin (10U), vancomycin (30 µg), erythromycin (15 µg), clindamycin (2 µg), linezolid (30 µg), tetracycline (30 µg), trimethoprim/sulfamethoxazole (1.25/23.75 µg), gentamicin (10 µg), ciprofloxacin (5 µg), and levofloxacin (5 µg). All disks were obtained from Oxoid Ltd. *S. aureus* ATCC25923 was used as quality control strain for antimicrobial susceptibility testing. The minimum inhibitory concentration of vancomycin was determined using the agar dilution method according to the guidelines of the CLSI.^{16,17}

Detection of Fusidic Acid Resistance Determinants by PCR

Isolates were tested for the presence of *fusB* and *fusC* by PCR, as previously described.¹⁸ Then, the amplified DNA fragments were sequenced for further confirmation.

Multi-Locus Sequence Typing (MLST)

Multi-locus sequence typing for *S. epidermidis* isolates was performed by amplification of internal fragments of the seven housekeeping genes including *arcC*, *aroE*, *gtr*, *mutS*, *pyrR*, *tpiA*, and *yqiL* of *S. epidermidis* as described previously.¹⁹ The PCR products of seven housekeeping genes tested for MLST typing were purified and sequenced. The numbers of alleles and sequence types were assigned using online database (<http://sepidermidis.mlst.net/>). The eBURST algorithm was used to infer the evolutionary relatedness of the STs.

Staphylococcal Cassette Chromosome (SCCmec) Typing

Primers for SCCmec typing were designed according to literature.²⁰ The 8 pairs of primers of *CCr* gene were CIE, KDP, MECI, DCS, RIF4, RIF5 and PUB110R1, and the 8 pairs of primers (Type I ~ Type V) sequence were detected for *mec* complex. The strains harmany21 (SCCmec I), harmany24 (SCCmec II), harmany20 (SCCmec III), harmany22 (SCCmec IV) and HS662 (SCCmec V) of SCCmec were used as positive control for SCCmec typing.

Pulsed-Field Gel Electrophoresis (PFGE)

Our test was slightly modified from the previously described method.²¹ The restriction enzyme *SmaI* was used and the following electrophoresis conditions: switch time, 4 s to 40s; running time, 19 h in a 1% agarose gel.

Results

A total of 711 strains of *Staphylococcus epidermidis* isolated from patients with clinical and infectious symptoms were considered for invasive isolates and included in the investigation. Among 711 *S. epidermidis* isolates, 55 (7.7%) FA-resistant *S. epidermidis* were isolated from blood (n = 18), catheter (n = 14), sputum (n = 5), ascites (n = 3), tissue (n = 3), drainage (n = 2), wound exudate (n = 2), urine (n = 2), dialysate (n = 2), marrow (n = 1), and other sources (n = 2).

Antimicrobial Susceptibility of FA-Resistant *S. epidermidis* Clinical Isolates

The distribution of FA MIC levels among FA-resistant *S. epidermidis* is shown in Table 1. The MIC values ranging from 4 to 32 µg/mL were resistant to FA. Among 55 isolates, 50 (90.9%, 50/55) and 5 (9.1%, 5/55) FA-resistant isolates were MRSE and MSSE, respectively. Besides FA resistance, the 55 *S. epidermidis* were also resistant to non-beta-lactam antimicrobials as shown in Table 2. The FA-resistant isolates exhibited more than 50% of resistance rates to erythromycin (n = 44), clindamycin (n = 36), trimethoprim-sulfamethoxazole (n = 36) and ciprofloxacin (n = 35), but less than 50% of resistance rates to others including gentamicin (n = 27), rifampin (n = 26) and tetracycline (n = 13). All 55 isolates mentioned above were susceptible to vancomycin and linezolid.

Detection of FA Resistance Determinants

Among 55 *S. epidermidis* isolates with FA resistance, 47 (85.5%) and 4 (7.3%) were positive for *fusB* and *fusC*, respectively. However, no resistance genes were detected in four strains.

Table 1 Distribution of FA MIC Levels in *S. epidermidis* Isolates

No. of <i>S. epidermidis</i> (%)	No. of Isolates with Different Fusidic Acid MIC (µg/mL)			
	4	8	16	32
55	2 (3.6%)	7 (12.7%)	39 (71.0%)	7 (12.7%)

Table 2 Prevalence of Antibiotic Resistance in FA-Resistant *S. epidermidis*

Antibiotics	FA-Resistant <i>S. epidermidis</i> (%)
Erythromycin	44 (80.0)
Clindamycin	36 (65.5)
Trimethoprim-sulfamethoxazole	36 (65.5)
Ciprofloxacin	35 (63.6)
Gentamicin	27 (49.1)
Rifampin	26 (47.3)
Tetracycline	13 (23.6)

Molecular Characteristics of *S. epidermidis* Clinical Isolates with FA Resistance

PCR was used to amplify *arcC*, *aroE*, *gtr*, *mutS*, *pyrR*, *tpi* and *yqiL* genes from 55. Strains of FA resistant *Staphylococcus epidermidis*. The molecular characteristics of the 55 FA-resistant *S. epidermidis* isolates are listed in Figure 1. A total of 14 STs

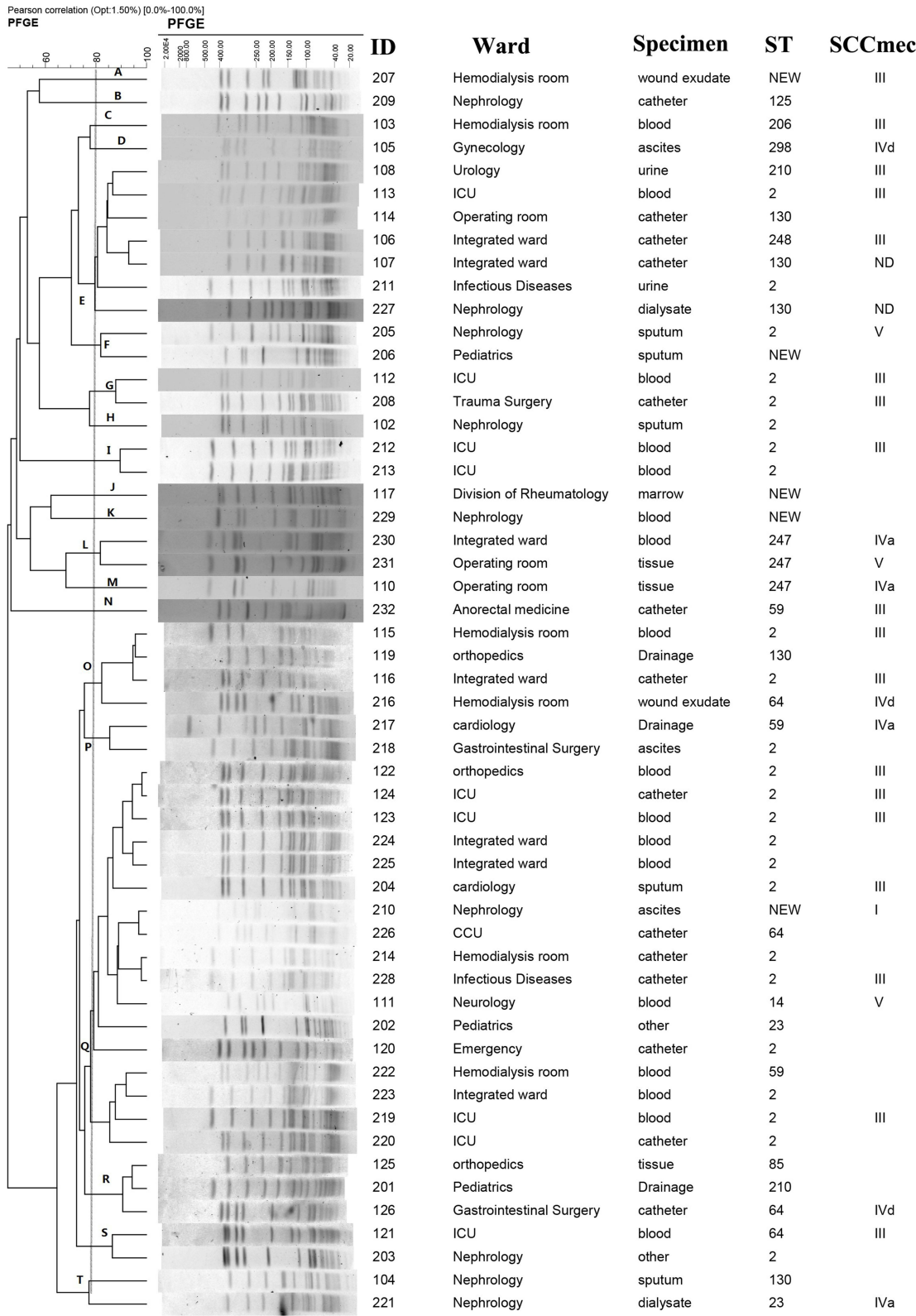


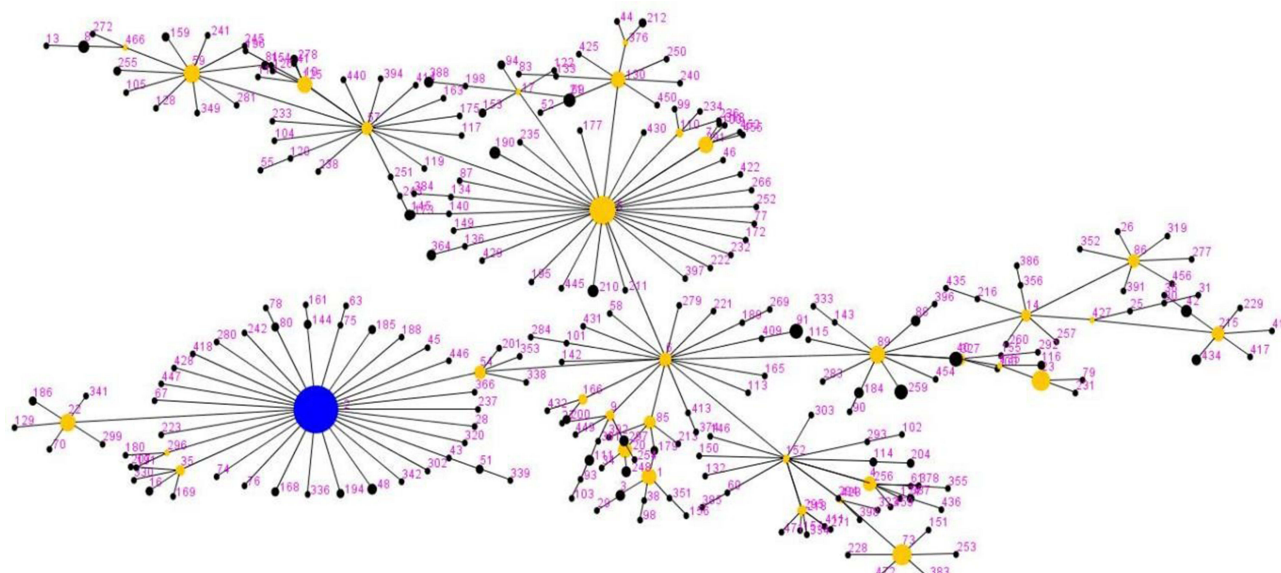
Figure 1 Results of PFGE and molecular characteristics of FA-resistant *S. epidermidis* isolates.

Table 3 The Comparison of Drug Resistance Between ST2 Type and Non-ST2 in FA-Resistant *S. epidermidis*

Antimicrobial Agents	ST2 N=24 R (n)	Non-ST2 N=31 R (n)
Tetracycline	0.0% (0)	41.9% (13)
Gentamicin	91.7% (22)	16.1% (9)
Penicillin	100.0% (24)	96.7% (30)
Clindamycin	66.7% (16)	67.6% (21)
Erythromycin	62.5% (15)	96.7% (30)
Ciprofloxacin	95.8% (23)	9.6% (3)
Linezolid	0.0% (0)	0.0% (0)
Rifampicin	91.7% (22)	12.9% (4)
Trimethoprim-sulfamethoxazole	91.7% (22)	41.9% (13)
Levofloxacin	91.7% (22)	12.9% (4)
Vancomycin	0.00% (0)	0.00% (0)
Moxifloxacin	54.2% (13)	3.2% (1)

were identified among the 55 *S. epidermidis* isolates with FA resistance, among which ST2 was the most prevalent, accounting for 43.7% (24/55), followed by ST130 (9.1%, 5/55), ST64 (7.3%, 4/55), ST59 (5.5%, 3/55), ST210 (3.6%, 2/55) and ST23 (3.6%, 2/55). Other STs was only found one isolate each, such as ST125. The STs for five isolates were not identified. In the study, ST2 was the most prevalent so that the comparison of drug resistance between ST2 and non-ST2 strains is presented in Table 3. The resistance profiles of 24 ST2 *S. epidermidis* isolates were similar that they were resistance to penicillin, ciprofloxacin, levofloxacin, gentamicin and trimethoprim-sulfamethoxazole, however, susceptibility to vancomycin, linezolid and tetracycline.

According to the 448 ST models in the MLST database, the eBURST software analysis was performed, and the 55 clinical isolates in this study were analyzed by eBURST algorithm. Most of the isolates belonged to SCCmec III (n = 18), while 4, 3, 3 and 1 isolates belonged to SCCmec IVa, SCCmec IVd, SCCmec Vand SCCmec I, respectively. Intriguingly, half of the 24 ST2 strains were SCCmec III, and only one strain was SCCmec V. It was found that most of the strains in the clinical isolates belonged to CC2, accounting for 43.7% (24/55), while 15 and 8 strains belonged to CC5 and CC247, respectively. The founder of the clinical isolates found in this study was ST2, which was consistent with the founder found in the analysis of the *S. epidermidis* global database, and ST5 has the largest number in the subgroup founder, which was the single-locus variant (SLV) of ST2 (Figure 2).

**Figure 2** The value represents the ST type name, the blue point is the CC type Founder, the yellow dot is Subgroup founder, the black dot is all other ST types, and the dot size indicates the number of CC types. The solid line between the two points indicates that there is only one housekeeping gene difference between the two ST types.

Results of Pulsed Field Gel Electrophoresis (PFGE)

According to the band analysis of pulsed field gel electrophoresis, the clones with more than 80% similarity were divided into 20 types (A-T) (Figure 1), showing considerable diversity. Seventeen isolates including 12 ST2 isolates (70.6%, 12/17) belonged to PFGE Q type, indicating clonal dissemination of *S. epidermidis* isolates with FA resistance. Of 12 ST2 isolates with same PFGE type isolated from blood (6), catheter (5) and sputum (1) mainly distributed in ICU and comprehensive disease area. Seven isolates including 3 ST130, 2 ST2, 1 ST248 and 1 ST210 isolates belonged to PFGE type E. These 7 isolates with same PFGE type were isolated from catheter (3), urine (2), blood (1) and peritoneal dialysate (1), respectively.

Discussion

Staphylococcus epidermidis, as a conditional pathogen, often causes a series of infections in people with low immunity or in infants and the elderly. To understand the origin of FA-resistant *S. epidermidis* and monitor them from different sources, analysis of molecular characteristics was performed in our study.

Chen et al found that the majority of FA-resistant *S. epidermidis* isolates were also resistant to methicillin.²² Our result was consistent with the above study that Methicillin-resistant *Staphylococcus epidermidis* was the predominates. McLaws et al reported a high prevalence rate (46%, 23/50) of resistance to fusidic acid in *S. epidermidis* clinical isolates.¹² Twenty-five percent of methicillin-resistant CNS and 15% of methicillin susceptible CNS strains isolated from blood cultures of septicemic patients in Turkey were resistant to FA.²³ Compared with the reports mentioned above, the prevalence of FA in the present study was relatively low.

Two major FA resistance mechanisms were reported, the alteration of the drug target site caused by the mutations in *fusA* encoding elongation factor G (EF-G) or *rplF* encoding ribosome protein L6 and the protection of the drug target site by *fusB* family proteins including *fusB*, *fusC*, and *fusD*, which have been reported in *S. aureus*.⁴ In *Staphylococci*, high-level FA resistance is usually associated with mutations in *fusA*, while low-level resistance is generally caused by plasmid-mediated resistance genes including *fusB*, *fusC* and *fusD*.²⁴ In the present study, 47 FA-resistant *S. epidermidis* clinical isolates were positive for *fusB*, while only four were positive for *fusC*. Colonized *Staphylococci* on skin may be reservoir for fusidic acid resistance genes.²⁵ The monitor for presence of fusidic acid resistance genes among *S. epidermidis* should be helpful for preventing the dissemination of FA-resistant *S. epidermidis*.

So far, a total of 448 ST types of *S. epidermidis* have been found worldwide. The main ST types of FA-resistant *S. epidermidis* in the drug resistance spectrum were ST2, ST130, ST64 and ST59. Studies had shown that ST2 was the main ST type of clinical isolates of *S. epidermidis* in the reports in the United States, Germany and other countries.^{26,27} In our study, ST2 was also found to be the most prevalent clone among *S. epidermidis* isolates with FA resistance, which was consistent with the main ST type of *S. epidermidis* found in other countries. In the present study, 24 ST2 MRSE with FA resistance isolated from blood, catheter, sputum, urine and ascites distributed among 9 wards, indicating that ST2 *S. epidermidis* clone with FA resistance has disseminated in this hospital. The drug resistance rate of ST2 to gentamicin, ciprofloxacin, rifampicin, levofloxacin and moxifloxacin was more than 5 times higher than that of non-ST2. A report from China showed that 91.7% (297/324) of *S. epidermidis* from the community and hospital environments belonged to CC2.¹⁵ CC2 comprises 74% of the *S. epidermidis* isolates from 17 national centers between 1996 and 2001.¹⁴ The majority (62/71; 87.3%) of *S. epidermidis* clinical isolates from US hospitals belonged to CC2.²⁸ We speculate that acquiring resistance to FA, as well as multi-resistance to other antimicrobial agents, contributes to the spread of *S. epidermidis* ST2 clone. ST23 was found among linezolid-resistant *S. epidermidis* isolates.^{29,30} In the present study, ST23 was identified in 2 *S. epidermidis* isolates with resistance to FA, which was first found among *S. epidermidis* isolates isolated from China. Although ST125 exist in online database (<http://sepidermidis.mlst.net/>), the literatures about *S. epidermidis* ST125 isolates was not found. The present study first reported ST125 among *S. epidermidis* clinical isolates. Taken together, the dissemination of *S. epidermidis* ST2 clone with FA resistance can cause trouble in controlling *S. epidermidis* infections.

In addition, although the results of PFGE for the 55 strains showed considerable diversity (20 PFGE types), 17 isolates including 12 ST2 isolates belonged to PFGE Q type, indicating clonal dissemination of *S. epidermidis* isolates with FA resistance has occurred. Clonal dissemination was the main reason for the cross-medical structure, cross-regional and even transnational global epidemic of *S. epidermidis*. Therefore, the etiological methods of tracking and monitoring

strains should clarify the homology and clonal dissemination of *S. epidermidis* strains timely and accurately at the type, subtype and molecular level, so as to effectively control the nosocomial infection of *Staphylococcus epidermidis* and the cloning and dissemination of bacterial drug resistance genes.

Ethics Statement

As the *Staphylococcus epidermidis* clinical isolates in this study were a part of the routine hospital laboratory procedure, the Ethics Committee of the first Affiliated Hospital of Wenzhou Medical University exempted this research for review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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