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# Activity of Fusidic Acid Tested against Staphylococci Isolated from Patients in U.S. Medical Centers in 2014

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**Fusidic acid (FA) activity was evaluated against 2,002 clinical staphylococcal isolates collected in U.S. hospitals during 2014. FA ($MIC_{50/90}$, 0.12/0.12 μg/ml) inhibited 99.8% of *Staphylococcus aureus* isolates at ≤1 μg/ml. Only four *S. aureus* isolates displayed FA values of >2 μg/ml (three strains with *fusC* and one with an L461K substitution in *fusA*), and they were isolated from patients in four states. In conclusion, FA demonstrated sustained, potent activity against this recent collection of U.S. staphylococci.**

*Staphylococcus* spp., especially *Staphylococcus aureus*, are a common cause of serious infections with multidrug resistance (MDR), and these species have emerged as a major therapeutic challenge throughout the world (1, 2). The global emergence of methicillin-resistant *S. aureus* (MRSA) (3) and strains with reduced vancomycin susceptibility (4, 5) have limited treatment options. For orally available antistaphylococcal agents, surveillance in the United States in 2013 found fluoroquinolone (levofloxacin), erythromycin, and clindamycin resistance rates of 64.2%, 87.8%, and 26.7%, respectively, among MRSA isolates, with an overall MRSA prevalence of 47.9% (6).

Due to these resistance issues, older agents with activity against MRSA are being reconsidered (7). One such agent with proven antistaphylococcal activity is fusidic acid (7, 8). Fusidic acid has been used in Europe and Australia since 1962 and in Canada since 1980 (8, 9) but has not been approved for clinical use by the U.S. Food and Drug Administration. Fusidic acid, with low toxicity and a unique mechanism of action (elongation factor G [EF-G]) that lacks significant cross-resistance to other antibacterial classes, is regarded as a potentially valuable therapeutic option in the United States, which has very low rates of fusidic acid resistance (8–10). Fusidic acid resistance has been described via mutations in the EF-G-encoding gene (*fusA*) or more recently described mobile elements (*fusB* and *fusC*). An intrinsic resistance gene, *fusD*, is found in *Staphylococcus saprophyticus* isolates (10).

Phase 2 clinical development of fusidic acid has concluded in the United States for the treatment of acute bacterial skin and skin structure infections (ABSSSI) (11) and chronic prosthetic joint infections (PJI) (12). A phase 3 trial in ABSSSI and an exploratory phase 3 study in refractory bone and joint infections (BJI) are being initiated. In this clinical development plan, a novel oral dosing regimen is being utilized to optimize bioavailability and exposure, hence reducing the potential for resistance emergence (13). When used with rifampin to minimize the potential for resistance development in a phase 2 trial, expected fusidic acid plasma levels were decreased, presumably by rifampin CYP3A induction, thus compromising optimal fusidic acid exposures (12).

In the present study, we report on the results of a U.S. resistance surveillance program, comparing the activity of fusidic acid and other antimicrobial agents against clinical isolates of *S. aureus* ($n$ = 1,804) and coagulase-negative staphylococci (CoNS) ($n$ = 198) obtained from patients in 2014.

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**TABLE 1** Antimicrobial activity of fusidic acid tested against contemporary staphylococcal clinical isolates from the United States, 2014

| Organism[a] | No. of isolates | No. of isolates (cumulative %) inhibited at MIC (μg/ml) of: | | | | | | | | | | | $MIC_{50}$ | $MIC_{90}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ≤0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | ≥16 | | |
| *S. aureus* | 1,804 | 1 (0.1) | 42 (2.4) | 773 (45.2) | 946 (97.7) | 31 (99.4) | 4 (99.6) | 3 (99.8) | 0 (99.8) | 2 (99.9) | 1 (>99.9) | 1 (100.0) | 0.12 | 0.12 |
| MSSA | 956 | 1 (0.1) | 23 (2.5) | 397 (44.0) | 515 (97.9) | 14 (99.4) | 2 (99.6) | 0 (99.6) | 0 (99.6) | 2 (99.8) | 1 (99.9) | 1 (100.0) | 0.12 | 0.12 |
| MRSA | 848 | | 19 (2.2) | 376 (46.6) | 431 (97.4) | 17 (99.4) | 2 (99.6) | 3 (100.0) | | | | | 0.12 | 0.12 |
| CoNS[b] | 198 | | 11 (5.6) | 101 (56.6) | 65 (89.4) | 2 (90.4) | 0 (90.4) | 0 (90.4) | 5 (92.9) | 6 (96.0) | 8 (100.0) | | 0.06 | 0.25 |
| MSCoNS | 58 | | 2 (3.4) | 33 (60.3) | 22 (98.3) | 1 (100.0) | | | | | | | 0.06 | 0.12 |
| MRCoNS | 140 | | 9 (6.4) | 68 (55.0) | 43 (85.7) | 1 (86.4) | 0 (86.4) | 0 (86.4) | 5 (90.0) | 6 (94.3) | 8 (100.0) | | 0.06 | 2 |

[a] MSSA, methicillin (oxacillin)-susceptible *S. aureus*; MRSA, methicillin (oxacillin)-resistant *S. aureus*; CoNS, coagulase-negative staphylococci; MSCoNS, methicillin (oxacillin)-susceptible CoNS; MRCoNS, methicillin (oxacillin)-resistant CoNS.
[b] Includes *S. capitis* (12 strains), *S. caprae* (3 strains), *S. cohnii* (1 strain), *S. epidermidis* (108 strains), *S. haemolyticus* (14 strains), *S. hominis* (14 strains), *S. intermedius* (2 strains), *S. lugdunensis* (25 strains), *S. pseudintermedius* (1 strain), *S. saprophyticus* (6 strains), *S. simulans* (7 strains), *S. warneri* (4 strains), and *Staphylococcus* species isolates that were not identified to the species level (1 strain).

**TABLE 2** Antimicrobial activity of fusidic acid and 10 comparator antimicrobial agents tested against staphylococci from the United States, 2014

| Antimicrobial agent | MIC (μg/ml) | | | S/I/R (%)[a] | |
|---|---|---|---|---|---|
| | $MIC_{50}$ | $MIC_{90}$ | Range | CLSI | EUCAST |
| *S. aureus* ($n$ = 1,804) | | | | | |
| Fusidic acid | 0.12 | 0.12 | ≤0.015 to >16 | –/–/– | 99.8/–/0.2 |
| Erythromycin | 16 | >16 | ≤0.12 to >16 | 40.2/5.9/53.9 | 40.4/1.5/58.1 |
| Clindamycin | ≤0.25 | >2 | ≤0.25 to >2 | 83.5/0.2/16.3 | 83.3/0.2/16.5 |
| Vancomycin | 1 | 1 | 0.25 to 2 | 100.0/0.0/0.0 | 100.0/–/0.0 |
| Linezolid | 1 | 1 | 0.25 to >8 | 99.9/–/0.1 | 99.9/–/0.1 |
| Oxacillin | 1 | >2 | ≤0.25 to >2 | 53.0/–/47.0 | 53.0/–/47.0 |
| Tetracycline | ≤0.5 | ≤0.5 | ≤0.5 to >8 | 94.9/0.3/4.8 | 92.3/1.5/6.2 |
| Gentamicin | ≤1 | ≤1 | ≤1 to >8 | 97.7/0.2/2.1 | 97.6/–/2.4 |
| Levofloxacin | 0.25 | >4 | ≤0.12 to >4 | 63.4/0.6/36.0 | 63.4/0.6/36.0 |
| TMP-SMX[b] | ≤0.5 | ≤0.5 | ≤0.5 to >4 | 97.9/–/2.1 | 97.9/0.1/1.9 |
| Daptomycin | 0.25 | 0.5 | ≤0.06 to 2 | 99.9/–/– | 99.9/–/0.1 |
| MSSA ($n$ = 956) | | | | | |
| Fusidic acid | 0.12 | 0.12 | ≤0.015 to >16 | –/–/– | 99.6/–/0.4 |
| Erythromycin | 0.25 | >16 | ≤0.12 to >16 | 64.4/7.5/28.1 | 64.7/2.3/33.0 |
| Clindamycin | ≤0.25 | ≤0.25 | ≤0.25 to >2 | 94.9/0.1/5.0 | 94.7/0.2/5.1 |
| Vancomycin | 1 | 1 | 0.5 to 2 | 100.0/0.0/0.0 | 100.0/–/0.0 |
| Linezolid | 1 | 1 | 0.25 to 2 | 100.0/–/0.0 | 100.0/–/0.0 |
| Tetracycline | ≤0.5 | ≤0.5 | ≤0.5 to >8 | 96.1/0.2/3.7 | 94.4/0.3/5.2 |
| Gentamicin | ≤1 | ≤1 | ≤1 to >8 | 99.2/0.0/0.8 | 99.0/–/1.0 |
| Levofloxacin | 0.25 | 2 | ≤0.12 to >4 | 90.0/0.4/9.6 | 90.0/0.4/9.6 |
| TMP-SMX | ≤0.5 | ≤0.5 | ≤0.5 to >4 | 99.2/–/0.8 | 99.2/0.0/0.8 |
| Daptomycin | 0.25 | 0.5 | ≤0.06 to 1 | 100.0/–/– | 100.0/–/0.0 |
| MRSA ($n$ = 848) | | | | | |
| Fusidic acid | 0.12 | 0.12 | 0.03 to 1 | –/–/– | 100.0/–/0.0 |
| Erythromycin | >16 | >16 | ≤0.12 to >16 | 12.9/4.1/83.0 | 13.1/0.5/86.4 |
| Clindamycin | ≤0.25 | >2 | ≤0.25 to >2 | 70.6/0.4/29.0 | 70.5/0.1/29.4 |
| Vancomycin | 1 | 1 | 0.25 to 2 | 100.0/0.0/0.0 | 100.0/–/0.0 |
| Linezolid | 1 | 1 | 0.25 to >8 | 99.9/–/0.1 | 99.9/–/0.1 |
| Tetracycline | ≤0.5 | 1 | ≤0.5 to >8 | 93.6/0.5/5.9 | 90.0/2.8/7.2 |
| Gentamicin | ≤1 | ≤1 | ≤1 to >8 | 96.1/0.4/3.5 | 96.0/–/4.0 |
| Levofloxacin | 4 | >4 | ≤0.12 to >4 | 33.5/0.7/65.8 | 33.5/0.7/65.8 |
| TMP-SMX | ≤0.5 | ≤0.5 | ≤0.5 to >4 | 96.6/–/3.4 | 96.6/0.3/3.1 |
| Daptomycin | 0.25 | 0.5 | ≤0.06 to 2 | 99.8/–/– | 99.8/–/0.2 |
| CoNS[c] ($n$ = 198) | | | | | |
| Fusidic acid | 0.06 | 0.25 | 0.03 to 8 | –/–/– | 90.4/–/9.6 |
| Erythromycin | 16 | >16 | ≤0.12 to >16 | 41.4/2.0/56.6 | 42.4/1.0/56.6 |
| Clindamycin | ≤0.25 | >2 | ≤0.25 to >2 | 70.2/2.5/27.3 | 66.7/3.5/29.8 |
| Vancomycin | 1 | 2 | 0.5 to 4 | 100.0/0.0/0.0 | 100.0/–/0.0 |
| Linezolid | 0.5 | 0.5 | 0.25 to >8 | 99.0/–/1.0 | 99.0/–/1.0 |
| Oxacillin | 1 | >2 | ≤0.25 to >2 | 29.3/–/70.7 | 29.3/–/70.7 |
| Tetracycline | ≤0.5 | >8 | ≤0.5 to >8 | 84.3/2.2/13.6 | 77.8/4.5/17.7 |
| Gentamicin | ≤1 | >8 | ≤1 to >8 | 80.8/3.0/16.2 | 76.8/–/23.2 |
| Levofloxacin | 0.25 | >4 | ≤0.12 to >4 | 60.6/0.0/39.4 | 60.6/0.0/39.4 |
| TMP-SMX | ≤0.5 | >4 | ≤0.5 to >4 | 76.8/–/23.2 | 76.8/12.7/10.6 |
| Daptomycin | 0.25 | 0.5 | ≤0.06 to 1 | 100.0/–/– | 100.0/–/0.0 |
| MSCoNS ($n$ = 58) | | | | | |
| Fusidic acid | 0.06 | 0.12 | 0.03 to 0.25 | –/–/– | 100.0/–/0.0 |
| Erythromycin | ≤0.12 | >16 | ≤0.12 to >16 | 70.7/1.7/27.6 | 70.7/1.7/27.6 |
| Clindamycin | ≤0.25 | 0.5 | ≤0.25 to >2 | 93.1/1.7/5.2 | 89.7/3.3/6.9 |
| Vancomycin | 1 | 2 | 0.5 to 2 | 100.0/0.0/0.0 | 100.0/–/0.0 |
| Linezolid | 0.5 | 0.5 | 0.25 to 1 | 100.0/–/0.0 | 100.0/–/0.0 |
| Tetracycline | ≤0.5 | 8 | ≤0.5 to >8 | 89.7/1.7/8.6 | 86.2/1.7/12.1 |
| Gentamicin | ≤1 | ≤1 | ≤1 to >8 | 98.3/0.0/1.7 | 96.6/–/3.4 |
| Levofloxacin | 0.25 | >4 | ≤0.12 to >4 | 75.9/0.0/24.1 | 75.9/0.0/24.1 |
| TMP-SMX | ≤0.5 | 4 | ≤0.5 to >4 | 87.9/–/12.1 | 87.9/5.1/6.9 |
| Daptomycin | 0.25 | 0.5 | ≤0.06 to 1 | 100.0/–/– | 100.0/–/0.0 |

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**TABLE 2** (Continued)

| Antimicrobial agent | MIC (μg/ml) | | | S/I/R (%)[a] | |
|---|---|---|---|---|---|
| | $MIC_{50}$ | $MIC_{90}$ | Range | CLSI | EUCAST |
| MRCoNS ($n$ = 140) | | | | | |
| Fusidic acid | 0.06 | 2 | 0.03 to 8 | –/–/– | 86.4/–/13.6 |
| Erythromycin | >16 | >16 | ≤0.12 to >16 | 29.3/2.1/68.6 | 30.7/0.7/68.6 |
| Clindamycin | ≤0.25 | >2 | ≤0.25 to >2 | 60.7/2.9/36.4 | 57.1/3.6/39.3 |
| Vancomycin | 1 | 2 | 0.5 to 4 | 100.0/0.0/0.0 | 100.0/–/0.0 |
| Linezolid | 0.5 | 0.5 | 0.25 to >8 | 98.6/–/1.4 | 98.6/–/1.4 |
| Tetracycline | ≤0.5 | >8 | ≤0.5 to >8 | 82.1/2.2/15.7 | 74.3/5.7/20.0 |
| Gentamicin | ≤1 | >8 | ≤1 to >8 | 73.6/4.3/22.1 | 68.6/–/31.4 |
| Levofloxacin | 0.5 | >4 | ≤0.12 to >4 | 54.3/0.0/45.7 | 54.3/0.0/45.7 |
| TMP-SMX | ≤0.5 | >4 | ≤0.5 to >4 | 72.1/–/27.9 | 72.1/15.9/12.1 |
| Daptomycin | 0.25 | 0.5 | ≤0.06 to 1 | 100.0/–/– | 100.0/–/0.0 |

[a] Criteria as published by CLSI and EUCAST for susceptible (S), intermediate (I), and resistant (R) categories (15, 16). –, no criteria for the category.
[b] TMP-SMX, trimethoprim-sulfamethoxazole.
[c] Includes *S. capitis* (12 strains), *S. caprae* (3 strains), *S. cohnii* (1 strain), *S. epidermidis* (108 strains), *S. haemolyticus* (14 strains), *S. hominis* (14 strains), *S. intermedius* (2 strains), *S. lugdunensis* (25 strains), *S. pseudintermedius* (1 strain), *S. saprophyticus* (6 strains), *S. simulans* (7 strains), *S. warneri* (4 strains), and *Staphylococcus* species isolates that were not identified to the species level (1 strain).

Nonduplicated staphylococcal isolates ($n$ = 2,002) were collected prospectively from 26 U.S. medical centers. These isolates were recovered consecutively from patients with ABSSSI, bacteremia, and respiratory tract infections, and fewer isolates were collected from other sources of infection. Isolates were identified by the submitting laboratories and confirmed by JMI Laboratories (North Liberty, IA, USA) using standard bacteriological algorithms and methodologies, including matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry (Bruker Daltonics, Billerica, MA, USA) and 16S rRNA sequencing.

All isolates were tested by the broth microdilution method (14) using commercially prepared and validated panels (Thermo Fisher Scientific, Inc., Cleveland, OH, USA) in cation-adjusted Mueller-Hinton broth. Fusidic acid was obtained from Cempra, Inc. (Chapel Hill, NC USA). Interpretation of the MIC results was in accordance with published criteria (15, 16). Quality control strains included *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212.

As previously described, resistance mechanisms were detected by PCR (*fusB*, *fusC*, *fusD*) and sequencing (*fusA*, *fusE*) (17, 18). Pulsed-field gel electrophoresis (PFGE) was performed to determine genetic relatedness.

Among 1,804 *S. aureus* isolates, fusidic acid ($MIC_{50/90}$, 0.12/0.12 μg/ml) inhibited 99.8% of isolates at ≤1 μg/ml (Table 1). Using EUCAST breakpoint criteria (≤1 μg/ml), fusidic acid susceptibility rates were very high, regardless of the methicillin-susceptibility profile: 99.6% for methicillin-susceptible *S. aureus* (MSSA) and 100.0% for MRSA (16). Among comparator agents with available oral formulations, linezolid, clindamycin, tetracycline, and trimethoprim-sulfamethoxazole (TMP-SMX) demonstrated the highest susceptibility rates against *S. aureus* strains at 99.9%, 83.5%, 94.9%, and 97.9%, respectively (Table 2). Overall against *S. aureus*, susceptibility rates were higher for agents administered by the parenteral route, i.e., vancomycin (100.0%), daptomycin (99.9%), and gentamicin (97.7%). Only four *S. aureus* strains (0.22%) displayed fusidic acid values of >1 μg/ml. Three isolates (from patients in Iowa, New York, and Florida) were positive for acquired *fusC* and had MIC values of 4 to 8 μg/ml. One isolate (from a patient in Georgia) had an L461K substitution in *fusA* and an MIC of >16 μg/ml.

For the CoNS strains, 90.4% were inhibited by fusidic acid at MIC values of ≤1 μg/ml, and the activity against CoNS exhibited differences between the methicillin-susceptible (MS) and methicillin-resistant (MR) subsets. MSCoNS and MRCoNS displayed the same $MIC_{50}$ result of 0.06 μg/ml, whereas MRCoNS $MIC_{90}$ results were negatively influenced by the fusidic acid-nonsusceptible isolates (13.6% with MICs of >1 μg/ml). Fusidic acid resistance mechanisms found among CoNS isolates were *fusB* ($n$ = 9), *fusC* ($n$ = 3), *fusD* ($n$ = 6, *S. saprophyticus*), and a D597E substitution in *fusA* ($n$ =1). PFGE analyses showed that none of the CoNS strains were clonally related. Linezolid was the only orally administered comparator agent with wide coverage for CoNS isolates, inhibiting nearly all (99.0%) of the strains at the current breakpoint concentration (15). Clindamycin, TMP-SMX, and tetracycline demonstrated only modest activity against these pathogens (70.2%, 76.8%, and 84.3% susceptible, respectively).

Although fusidic acid has not been used clinically in the United States, it has exhibited clinical efficacy and low toxicity in the treatment of serious MRSA infections in many countries (5, 9, 19). However, fusidic acid used as topical monotherapy for chronic skin conditions has been associated with the emergence of resistance among *S. aureus* and CoNS in several nations, thus compromising its utility for both topical and systemic therapy (9, 20–26). PJI is the most serious complication of joint replacement surgery, and antimicrobial therapy is generally prolonged or indefinite. Initial therapy of 4 to 6 weeks of pathogen-specific intravenous or highly bioavailable oral therapy is followed by indefinite chronic oral antimicrobial suppression therapy based on *in vitro* susceptibility of the pathogen and patient allergies or intolerances. Therefore, monitoring for toxicity development and efficacy is highly recommended (27). Fusidic acid has many favorable attributes (e.g., low toxicity and high oral bioavailability) that make it a desirable candidate for the treatment of ABSSSI and for long-term treatment of BJI and PJI in the United States and elsewhere. In this report, we describe the results of a contemporary (2014) surveillance survey designed to assess fusidic acid activity against clinical isolates of staphylococci. Overall, fusidic acid demonstrated high *in vitro* potency against *S. aureus* ($MIC_{90}$, 0.12 μg/ml) and CoNS ($MIC_{90}$, 0.25 μg/ml), regardless of resistances to other antimicrobials. We detected only 4 (0.22%) *S. aureus* isolates and 19 (9.6%) CoNS isolates that displayed elevated fusidic acid values at >1

μg/ml. Mechanisms of resistance were also observed, without evidence of genetic relatedness. These recent U.S. results were very similar to U.S. resistance surveillance results in 2008, which showed only 0.3% of *S. aureus* isolates (0.6% in MRSA and 0.1% in MSSA) and 6.4% of CoNS isolates with resistance (fusidic acid MIC, >1 μg/ml) (18). As in the earlier study, the mechanisms responsible for fusidic acid resistance were quite varied, usually *fusB* and *fusC* (18, 28, 29).

The observed low prevalence of fusidic acid resistance among staphylococci in U.S. surveillance results between 2008 and 2014 documents a lack of resistance emergence or spread of clones during this 7-year period. The findings add further support and confidence to the continued clinical development of this orally available agent and provide a contemporary baseline of fusidic acid activity for the United States.

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