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**Background:** Fusidic acid (FA) is an established anti-staphylococcal agent used in clinical practice in Europe, Australia and Canada for at least three decades. FA is currently under clinical development in the USA. This study assessed the activities of FA and comparators tested against *Staphylococcus aureus*(SA) and coagulase-negative staphylococci (CoNS) isolates. Mutation analysis was performed by PCR and sequencing.

**Methods:** SA (1,804 isolates) and CoNS (193 isolates) were collected in 2014 from 26 medical centers located in the USA. Identification was performed by standard algorithms. Isolates were tested for susceptibility (S) by CLSI methods (M07-A10 and M100-S25). Resistance mechanisms were detected by PCR (*fusB*, *fusC*, *fusD*) and sequencing (*fusA*, *fusE*). PFGE was performed to determine clonality.

**Results:** FA (MIC<sub>50/90</sub>, 0.12/0.12 µg/mL) inhibited 99.8% (1800/1804) of the SA strains at ≤1µg/mL. Using EUCAST breakpoints, FA susceptibility rates were very high, regardless of the methicillin-susceptible/resistant profile (99.6% for MSSA and 100.0% for MRSA). Three SA strains, isolated from patients in Iowa, New York, and Florida were positive for *fusc* and had FA MICs of 4 to 8 µg/mL. One strain, from a patient from Georgia, had a L461K substitution in *fusA* and a FA MIC of >16 µg/mL. A total of 179 of the 193 (92.7%) CoNS strains were inhibited by FA at MIC values ≤1µg/mL. The activity of FA against CoNS demonstrated differences between the MS/MR subsets. MS-CoNS displayed MIC<sub>90</sub> results of 0.12µg/mL with all isolates inhibited at MIC values ≤0.25µg/mL, whereas the MIC<sub>90</sub> was 2µg/mL for MR-CoNS (representing 69.9% of strains). FA resistance mechanisms found in CoNS were (n): *fusB*(9), *fusC*(3), and D597E substitution in *fusA*(1). PFGE revealed that none of CoNS strains were clonally related –including strains found in the same medical center.

**Conclusion:** Compared to previous surveys, FA demonstrated sustained and potent activity against this current collection of staphylococci from USA hospitals. A variety of FA resistance mechanisms were found and epidemiology (demographics and PFGE) did not reveal any evidence of clonality.