



Case Commentary: Daptomycin Resistance in *Staphylococcus argenteus*—from Northern Australia to San Francisco

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ABSTRACT *Staphylococcus argenteus* infection was initially described in Aboriginal patients in the Northern Territories of Australia as a predominant cause of skin infections and is rare outside Southeast Asia. A first well-characterized case of *S. argenteus* infection has now been described in the United States, involving a recurrent hemodialysis catheter infection, in which unstable daptomycin resistance evolved during daptomycin therapy. The unique colonial pigmentation of *S. argenteus* isolates in strains otherwise identified as *Staphylococcus aureus* is noteworthy.

KEYWORDS *Staphylococcus argenteus*, daptomycin resistance

Among recent changes in microbiological taxonomy, *Staphylococcus aureus* is now recognized as an *S. aureus*-related complex, comprising *S. aureus*, *Staphylococcus argenteus*, and *Staphylococcus schweitzeri* (1). Key questions for clinicians relate to the degree with which the epidemiology, clinical manifestations, and response to therapy are similar or distinct between these species and, thus, whether respective infections should be managed differently. First observed as a divergent *S. aureus* genotype usually associated with skin infections in northern Australian Aboriginal populations (2), *S. argenteus* isolates have now been identified globally. As suggested by its name, *S. argenteus* does not demonstrate the typical golden colony appearance on laboratory culture because it lacks the gene operon for the carotenoid pigment staphyloxanthin (Fig. 1), giving it the characteristic white colonial phenotype (3). In retrospective analyses, the proportion of isolates previously identified as *S. aureus* that were in fact *S. argenteus* ranged from 0.16% (3/1,903) in Belgium (4) to 12% (47/394) among blood culture isolates in Taiwan (5) and 19% (58/311) of sepsis-related isolates in Thailand (6). *S. argenteus* infection is typically methicillin susceptible but is capable of acquiring genes mediating methicillin and other antibiotic resistances (5, 6). In fact, in the Australian Aboriginal populations (where antibiotic use is high), methicillin-resistant *S. argenteus* outnumbered methicillin-resistant *S. aureus* (MRSA) infections; moreover, *S. argenteus* isolates were more likely than MRSA isolates to be resistant to multiple antibiotic classes (7).

There are a number of noteworthy microbiological features in the case reported by Hao et al. (8). (i) This is the first well-described clinical case of *S. argenteus* infection in the United States. (ii) The strain was misidentified as methicillin-susceptible *S. aureus* by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS). With the inclusion of *S. argenteus* in some newer commercial MALDI-TOF MS databases, clinical microbiology laboratories should be able to distinguish *S. aureus* from *S. argenteus* isolates. However, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has recommended not distinguishing species within

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FIG 1 Comparison of colony pigmentation on chocolate agar for *Staphylococcus aureus* (left) and *Staphylococcus argenteus* (right). (Republished from reference 3 with permission of the publisher.)

the *S. aureus*-related complex for routine reporting until there is evidence that pathogenicity or clinical outcomes differ markedly between species (9). (iii) In contradistinction to the majority experience in northern Australia concerning *S. argenteus* infections among Aboriginal patients (in which nonbacteremic skin and soft tissue infections have predominated) (2), the current patient's clinical course featured health care-associated (hemodialysis catheter) bacteremia. To this point, although relatively uncommon, selected reports have confirmed invasive endovascular infections, including vascular graft syndromes, caused by *S. argenteus* (10). (iv) The microbiology laboratory in this medical center apparently did not observe the typical pure white colonies of *S. argenteus* isolates on their blood culture plates (Fig. 1). (v) Until the present report from Hao and colleagues (8), *S. argenteus* resistance to daptomycin or vancomycin was not documented. (vi) The emergence of a single nucleotide polymorphism mutation in the *mprF* gene (as delineated by whole-genome sequencing) accompanied the evolution of increased MICs to daptomycin into the nonsusceptible range (4 $\mu\text{g/ml}$).

The latter event would not be unexpected in this particular patient given the lack of source control in a probable high-inoculum infection (vascular device) plus the repetitive courses of daptomycin. Although the MprF mutation described (S337L) occurs within one of the classic bifunctional domain hot spots of this protein (11, 12), the instability of this mutation was surprising. As pointed out by the authors, in *S. aureus* (usually MRSA) infection, daptomycin nonsusceptibility is a stable phenotype, most frequently linked to acquisition of *mprF* mutations (13). This genetic phenomenon has been seen clinically (as in this case), complicating daptomycin therapy of high-inoculum infections occurring at anatomic sites that are notoriously difficult to eradicate (e.g., endocarditis, osteomyelitis) (13). In fact, when *S. aureus* strains are serially passaged *in vitro* in daptomycin, *mprF* mutations are invariably the first ones induced, followed by *rpoB,C* and *yycFG* (14). Most investigations have ascribed the mechanism(s) of daptomycin resistance related to *mprF* polymorphisms to be based in gain-in-function enhancement of lysinylation of phosphatidylglycerol in the cell membrane of

staphylococci, as well as its increased translocation of this positively charged phospholipid to the outer cell membrane leaflet (13, 15). This would, in turn, theoretically create a relatively more positively charged surface, with a resultant charge-repulsive milieu that could repel calcium-complexed daptomycin (15). However, recent data from Ernst et al. (11) have implicated a non-surface-charge-associated mechanism for daptomycin resistance in strains with *mprF* mutations, i.e., a specific cell membrane biophysical perturbation that appears to allow for selective daptomycin efflux. Unfortunately, the instability of the *mprF* mutation in the current *S. argenteus* infection precludes further understanding of the mechanism of daptomycin resistance in this case.

An unanswered question remains. Were there any other *S. argenteus* strains isolated temporally at their medical center in and around the time of this patient's multiple admissions? The same question may be asked concerning other hemodialysis patients at the inpatient or outpatient facilities utilized by this patient. The community and nosocomial life cycles of *S. argenteus* isolates are poorly understood; thus, any insights in this regard may be enlightening.

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