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Original Article

Staphylococcus epidermidis joint isolates: Whole-genome sequencing demonstrates evidence of hospital transmission and common antimicrobial resistance

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Abstract

Objective: We investigated genetic, epidemiologic, and environmental factors contributing to positive *Staphylococcus epidermidis* joint cultures.

Design: Retrospective cohort study with whole-genome sequencing (WGS).

Patients: We identified *S. epidermidis* isolates from hip or knee cultures in patients with 1 or more prior corresponding intra-articular procedure at our hospital.

Methods: WGS and single-nucleotide polymorphism–based clonality analyses were performed, including species identification, in silico multilocus sequence typing (MLST), phylogenomic analysis, and genotypic assessment of the prevalence of specific antibiotic resistance and virulence genes. Epidemiologic review was performed to compare cluster and noncluster cases.

Results: In total, 60 phenotypically distinct *S. epidermidis* isolates were identified. After removal of duplicates and impure samples, 48 isolates were used for the phylogenomic analysis, and 45 (93.7%) isolates were included in the clonality analysis. Notably, 5 *S. epidermidis* strains (10.4%) showed phenotypic susceptibility to oxacillin yet harbored *mecA*, and 3 (6.2%) strains showed phenotypic resistance despite not having *mecA*. *Smr* was found in all isolates, and *mupA* positivity was not observed. We also identified 6 clonal clusters from the clonality analysis, which accounted for 14 (31.1%) of the 45 *S. epidermidis* isolates. Our epidemiologic investigation revealed ties to common aspirations or operative procedures, although no specific common source was identified.

Conclusions: Most *S. epidermidis* isolates from clinical joint samples are diverse in origin, but we identified an important subset of 31.1% that belonged to subclinical healthcare–associated clusters. Clusters appeared to resolve spontaneously over time, suggesting the benefit of routine hospital infection control and disinfection practices.

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Prosthetic joint infection (PJI) complicating hip and knee arthroplasty results in medical morbidity, added cost, reoperation, and higher mortality.[1–3] The prevalence of hip and knee arthroplasty is increasing due to a rising number of procedures and an aging population. In the United States, ~10% of women and 8% of men aged in their 70s and 80s have a total knee replacement.[4] These factors contribute to an overall rising incidence of PJI.[5]

Staphylococcus epidermidis is among the most common causes of PJI in total joint arthroplasty.[6–8] Monomicrobial infections caused by *S. epidermidis* tend to manifest later than others and to present with more subtle clinical signs.[9,10] Thus, *S. epidermidis* infections often present after the 90-day surveillance recommended by the Nationwide Healthcare Safety Network/Centers for Diseases and Control and Prevention (NHSN/CDC) for surgical site infection (SSI), leading to underreporting.

S. epidermidis is a commensal skin organism. PJI is thought to be seeded at the time of surgery or later through injection or hematogenous spread.[11] A growing number of molecular studies have identified genetic traits that may differentiate pathogenic *S. epidermidis* from commensal strains.[12–14]

If there are other mechanisms of transmission of *S. epidermidis* in PJI, such as dominant community strains or nosocomial transmission, they have not been addressed by the existing literature and may be missed by routine surveillance given the indolent clinical presentation. Whole-genome sequencing (WGS) may provide insight into these common but understudied infections.[15–18] In this study, we performed molecular and clinical assessments of 4 years of consecutive *S. epidermidis* isolates

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obtained from prosthetic joints in an orthopedic hospital to better understand the origin of and risk for these infections.

Methods

Whole-genome sequencing was used to analyze a cohort of *S. epidermidis* isolates obtained from arthrocentesis and surgical joint cultures collected between January 1, 2017, and December 31, 2020. *S. epidermidis* isolates were collected through routine clinical practice. After receiving approval from the institutional review board, *S. epidermidis* isolates from patients with 1 or more prior corresponding intra-articular procedures at our hospital were identified using microbiology laboratory records and hospital medical records.

Collection of samples

Clinical specimens were processed in a Clinical Laboratory Improvement Amendments–certified microbiology laboratory. Samples were routinely incubated for 5 days, or 14 days upon clinician request. Microscan (Omron, Renton, WA) was used for strain identification of the clinical isolates and antibiotic susceptibility testing. Isolates were banked in a −80°C freezer as part of routine practices. The identified *S. epidermidis* samples were thawed and regrown under a laboratory fume hood and for 24 hours at 37°C. Individual colonies were added to thioglycolate broth or chocolate slants and were incubated again for 24 hours at 37°C prior to shipping to Day Zero Diagnostics (Boston, MA) for genomic analysis.

Preparation of bacterial genomic DNA and WGS library

Whole-genome sequencing was performed at Day Zero Diagnostics using the epiXact PRO service. Bacterial DNA from 60 isolates was purified using the DNAeasy Ultra Clean Microbial kit (Qiagen, Hilden, Germany) protocol according to the manufacturer's guidelines. The quality of extracted DNA of each sample was assessed using Nanodrop (Thermo Fisher Scientific, Waltham, MA) and was quantified using the Qubit dsDNA HS assay kit (Invitrogen, Carlsbad, CA). Genomic DNA libraries were prepared using Nextera tagmentation (Illumina, San Diego, CA) and were ligated with unique, dual-indexed (i5 and i7) primers during amplification. Tapestation 4150 (Agilent) dsDNA assay was used to estimate fragment size. Sample libraries were pooled based on fragment size and concentration for multiplexed sequencing on the Illumina MiniSeq and HiSeqX sequencers. In addition, 2×150-bp paired-end reads were generated and demultiplexed into FastQ-formatted sequencing data.

Genomic analysis

The single nucleotide polymorphism (SNP)–based clonality and WGS analysis included species identification, in silico multilocus sequence typing (MLST) typing, and phylogenomic analysis, along with genotypic assessment of the prevalence of specific antibiotic resistance genes, virulence genes, and other relevant genes. Kraken software was used for species identification. Samples with high level contamination (>10%) with other species were discarded from the clonality analysis. MLST was inferred in silico using the PubMLST database.[19] Samples were grouped by MLST and, for each group, a reference genome of matching MLST was identified from RefSeq and was used for read mapping and SNP calling. The de novo assemblies from each group were also used as reference to verify SNP calling or when no closely related reference was identified. Mapping metrics included percent reference genome covered (>95%) and percent mapped reads (>80%). SNP calling metrics included Phred score (>20) minimum depth (≥10 reads) and major allele frequency (>90%). A pairwise SNP analysis was performed within each MLST group. Insertions and deletions were not included in the SNP analysis. Recombination events were identified using Genealogies Unbiased By recomBinations In Nucleotide Sequences (GUBBINS) software.[20] Cluster isolates were defined as 2 or more isolates with a pairwise distance of <25 SNPs.[21]

The phylogenomic analysis was performed using an external reference genome (Genbank: GCA-002850315v1). The presence of genomic features of interest, both genes and markers, was assessed in each sample using the BLAST version 2.11 algorithm and sample assemblies. We used iTOL V6 for phylogenomic tree visualization.[22]

Epidemiologic data

Hospital electronic medical records were manually reviewed for patient demographics and environmental data including age, sex, and patient's town. The following surgical and procedure data were considered: operating room (1–16), personnel in procedure, inpatient unit, date of procedure, surgical instruments and implants, prosthesis versus native joint, revision versus primary surgery, and days between prior intervetion and culture positivity. PJI was determined using the Musculoskeletal Infection society (MSIS) criteria.[23,24] Additional reviews of surgical and clinical data including personnel, equipment and supplies, and hospital space were performed to compare cluster cases and noncluster cases. Univariate analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC). $P < .05$ was considered statistically significant.

Results

Between 2017 and 2020, 11,358 hip arthroplasties and 13,406 knee arthroplasties were performed. During this time, the deep and organ-space SSI incidence rate and SIRs remained at historical baselines for the hospital (Supplementary Fig. 1 online). Also, 60 *S. epidermidis* joint isolates were identified from 44 patients, including 35 patients with prosthetic joints. Of these 35 patients, 19 (54.3%) met MSIS criteria for PJI, and 9 (22.0%) met NHSN/CDC criteria for hip arthroplasty or knee arthroplasty. Of those who met the MSIS PJI criteria but not the NHSN/CDC organ-space SSI criteria, 6 patients presented outside the 90-day surveillance window, 2 patients did not meet the clinical criteria for infection, and 3 patients had no prior surgery at our institution.

The average age of the study participants was 61 years, and 22.2% were female. Moreover, 37.8% of the isolates were obtained from hip joints, and the rest were obtained from knee joints. Of 60 samples, 25 (41.7%) were polymicrobial, resulting in 7 multispecies or multistrain contaminated samples for which data cleanup was not possible. After removal of these 7 samples as well as 5 duplicate isolates (same infection, multiple specimen at different time points), 48 samples were ultimately included for phylogenomic analysis, and 45 (93.7%) of these samples were included in the clonality analyses (Fig. 1). In total, 25 distinct sequence types (STs) were identified. Among these 45 samples, 2 (4.4%) had no ST match in PubMLST.

Genomic sequencing revealed common genes in all isolates, including virulence and biofilm genes *sepA* and *cap*, and the staphylococcal multidrug resistance gene *smr*. Of the 48 isolates, 31 isolates (64.6%) had the *mecA* gene, but only 29 isolates (60.4%) had phenotypic oxacillin resistance. Also, 5 isolates (10.4%) were

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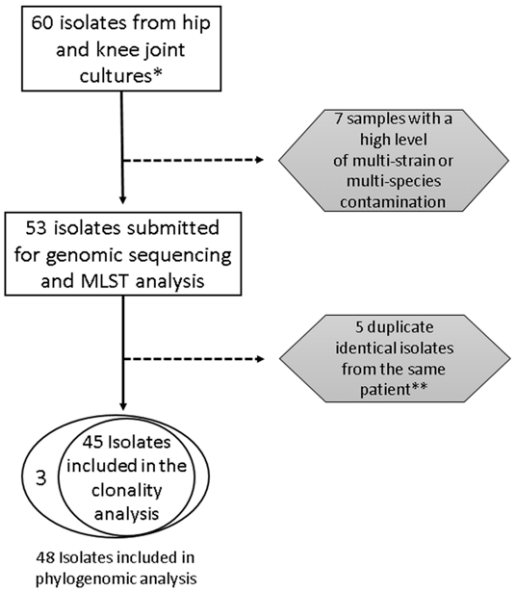

Figure 1. Flowchart of isolate selection. Hexagons represent isolates that were excluded. In total, 48 isolates were included in the final analysis (48 for phylogenomic analysis, 45 for clonality analysis). Of these 48 isolates, 3 were not included in the clonality analysis because of multistrain contamination. *From patients with at least 1 prior procedure in the same joint at our hospital. **Based on a SNP difference of 0; all patients from duplicate isolates met MSIS criteria for PJI.

phenotypically susceptible to oxacillin yet harbored *mecA,* and 3 isolates (6.2%) showed phenotypic resistance despite not having *mecA* (Fig. 2). *mecC* was not observed in any isolate.

Epidemiologic data revealed that most of these patients had a significant prior healthcare exposure (Table 1). Among the 45 patients, 17 (37.8%) had 2 or more same-joint surgeries prior to a positive culture, and 11 patients (28.9%) had 2 or more aspirations prior to a positive culture.

Among 45 strains included in the clonality analysis, we identified 6 distinct clusters of isolates. Cluster isolates accounted for 14 (31.1%) of all *S. epidermidis* joint isolates sequenced (Fig. 3). Also, 3 (21.4%) of the clonal *S. epidermidis* isolates and 1 (3.2%) of the nonclonal *S. epidermidis* isolates were obtained from native joints, and the rest were obtained from prosthetic joints. Each cluster of *S. epidermidis* clonal isolates comprised 2–4 different patients. The average number of days between the first and last clonal isolate in each cluster was 136 days (range, 25–330).

Further epidemiologic investigation showed that some of these clonal isolates had ties to aspirations or operative procedures occurring during a similar timeframe (Fig. 4). For several clusters, procedures were within weeks of each other, and others were months apart. None of the cluster cases shared common surgical instruments. One cluster involved 2 patients with the same anesthesiologist for surgeries that were performed 2 months apart. Some cluster isolates seemed to have no overlapping connection. Overall, no convincing factor was identified to account for hospital transmission, but aspirations in close chronological proximity appeared to be a relevant factor in some cases. In all cases, clusters appear to have been self-limited and resolved with standard infection control practices.

Discussion

This 4-year study of consecutive *S. epidermidis* joint isolates revealed a high degree of antimicrobial resistance and previously undescribed level of hospital transmission of *S. epidermidis*. *S. epidermidis* is one of the most common causes of PJI, yet relatively little is known about the transmission dynamics and molecular epidemiology of this organism. This study revealed several novel findings, including multiple clusters of hospital-acquired cases accounting for 14 (31%) of the 45 cases during a period of overall low surgical-site infection rates.

In addition, many isolates contained genetic resistance to common hospital disinfectants and antibiotics, perhaps yielding a competitive advantage in the hospital environment. These findings are supported by similar study results from Sweden. Researchers compared strains of *S. epidermidis* isolated from prosthetic joints with nasal strains. They found a high incidence of antimicrobial resistance in the infection isolates, but not the nasal isolates, indicating either selection of commensal resistant strains or acquisition of new strains during hospitalization.[25,26] In our study, a comprehensive outbreak investigation failed to identify specific epidemiologic links between the clonal *S. epidermidis* isolates although close temporal relationships in the care were observed. This finding suggests the possibility of reservoirs of *S. epidermidis* in healthcare settings. Because all analyses occurred in 2021 (1–5 years after the organisms were originally obtained) and no specific people, places, or objects were identified as possible modes of transmission, we did not attempt to search for these strains of *S. epidermidis* through WGS of random samples of the environment or staff.

Each cluster included 2–4 patients. Cluster cases differed by very few SNPs (Fig. 3), even when detected months apart. This finding suggests slow diversification and/or strain persistence, compared to the molecular clock and mutation rates of organisms such as *S. aureus*.[27,28] Compared to noncluster cases, cluster cases did not differ in any of the variables assessed (Table 1). However, both cluster and noncluster *S. epidermidis* cases were highly exposed to health care, which may have been a byproduct of our inclusion criteria. Clusters had a mean of 136 days (range, 25–330) between the first and last isolates in the cluster, and in some cases patients presented with infection months after the suspected transmission event or procedure. Thus, detection of these clusters was challenging in routine infection control surveillance. Indeed, during this time frame, the hospital had standardized infection ratios for hip and knee arthroplasties, which were statistically lower than national average, and there were no clinically detected PJI outbreaks from any organism.

All clusters were self-limited, suggesting that routine infection control practices were ultimately effective at eliminating the putative reservoir in all clonal cases. In hospital-acquired clonal bacterial spread, the possible modes of transmission of these isolates were 3-fold: (1) transmission from a common environmental reservoir to patients, (2) transmission from one patient to another (likely via an environmental reservoir or common healthcare worker), and (3) contamination of the microbiology laboratory.[12,29] A fourth possibility, endogenous acquisition in patients who acquired a common strain from community source outside the hospital, is less likely given the disparate geographic regions of cluster patients and diverse sequence types (STs) in the series. Importantly, the study inclusion criteria did not require that the patient meet clinical criteria for prosthetic joint infection, allowing better detection of clonal isolates. This further highlights the importance of universal infection control practices including environmental decontamination, equipment disinfection and sterilization, and hand hygiene.

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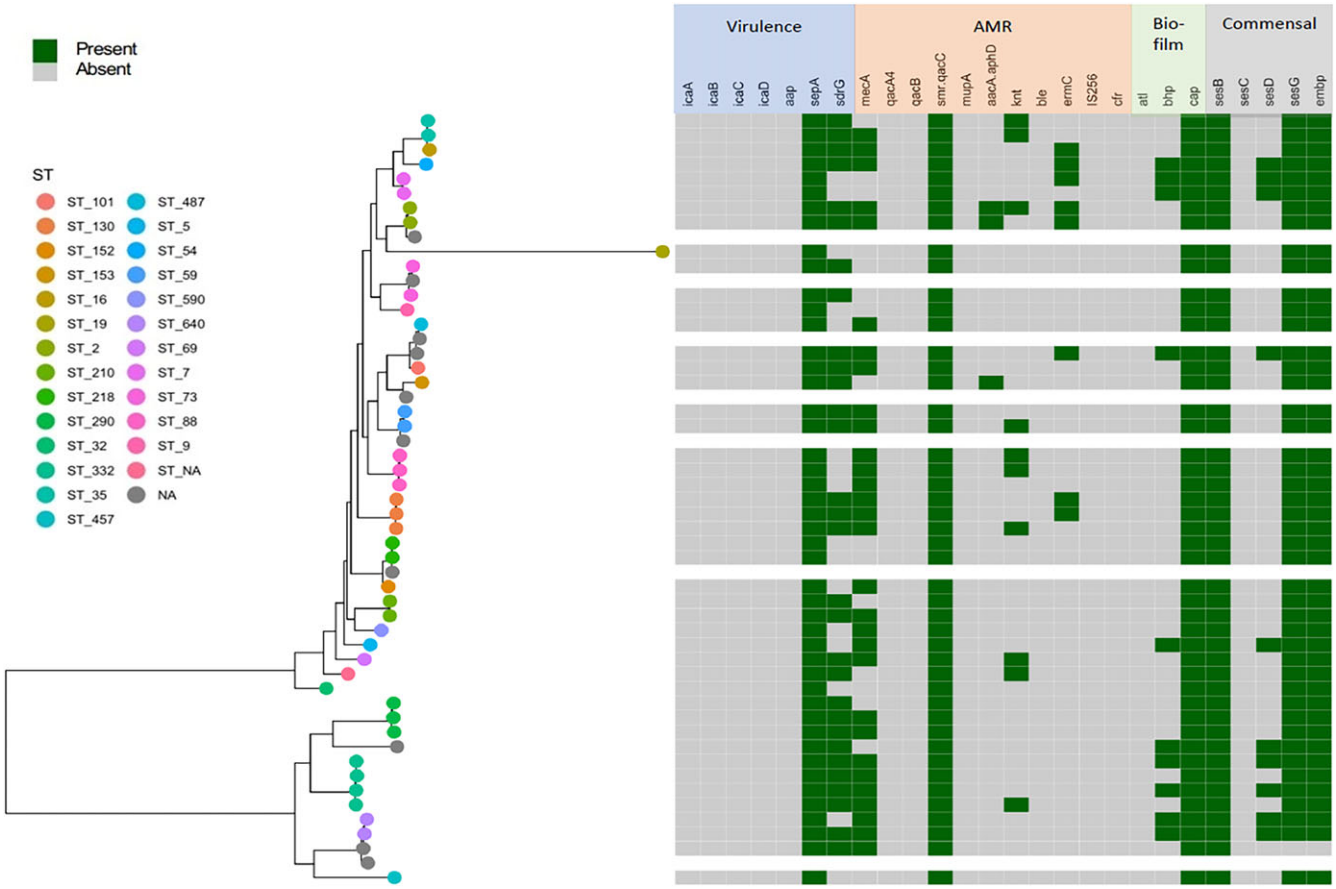

Figure 2. Phylogenetic structure and sequence types (left panel) of the *Staphylococcus epidermidis* population. Right panel showing gene presence or absence inferred from whole-genome sequencing de novo assemblies. Green cell corresponds to a full gene hit, and white cells to no hit. Only isolates included in both clonality analysis and phylogenetic analysis are shown. Note. AMR, antimicrobial resistance.

In this study, we assessed specific genes that may give *S. epidermidis* a competitive advantage in orthopedic infections. Of the genes selected, the most important findings were the presence of *mecA* and *smr*. *MecA* was present in 31 (64.6%) of 48 isolates, including 5 isolates that were phenotypically susceptible to β-lactams. Further investigation is required to better understand the significance of *mecA* positive, cefazolin-sensitive isolates, and implications for surgical prophylaxis and treatment. In addition, 100% of the isolates contained the *smr* gene, encoding an efflux pump that confers decreased susceptibility to quaternary ammonia compounds and other cationic substrates including common hospital disinfectants and potentially biguanides such as chlorhexidine.[30] In addition, we also observed a partial match for *qacA* and *qacB*, additional resistance determinants for quaternary ammonia compounds and biguanides. This finding raises a genetic basis of concern for emerging resistance to chlorhexidine in staphylococci, supporting similar findings from other studies in *Staphylococcus* spp.[25,26,31–34] In our arthroplasty population, our hospital has utilized a chlorhexidine and mupirocin decolonization protocol for preoperative arthroplasty patients with *S. aureus* colonization, as well as routine chlorhexidine decolonization for 2 days prior to surgery for all patients since 2005. Surgical skin preparation is achieved by either chlorhexidine/alcohol or iodine/alcohol.[35] Despite this longstanding protocol, mupirocin resistance (*mupA*) was not observed.

The STs represented in this study were diverse. STs previously identified as being associated with pathogenicity, including ST2 and ST215, were present, but the majority of STs in this study were from strains not previously linked with virulence or pathogenicity. Furthermore, no one strain dominated over others in this study. Prior research has also linked *ses* genes to commensal strains of *S. epidermidis*.[36,37] Our data do not support that *ses* genes are linked to pathogenicity or commensal strains in orthopedic infections.

This study was limited by the retrospective nature of the study design, which did not allow for real-time analysis of environmental or staff *S. epidermidis* strains. Thus, specific reservoir sources could not be determined. MSIS criteria were used to identify patients with PJI, but data were collected retrospectively and, in some cases, clinicians may not have ordered inflammatory markers or histology depending on clinical presentation. This factor could have artificially lowered the number of PJI in the sample. As part of our inclusion criteria, we only included patients with a prior procedure at our institution. We may have underestimated clonality if patients outside our inclusion criteria acted as a transmission reservoir. Furthermore, SNP thresholds for defining clonality are not well established for *S. epidermidis*, and variable strain clock rates and sample collection times can affect thresholds.[38] Nevertheless, the low SNP threshold used in this study is a conservative cutoff that falls below observed SNP distances of other staphylococci

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Table 1. Univariate Table of Select Patient Demographics, Healthcare History, and Infection information.

Variable	Total Isolates, No. (%)	Nonclonal Isolates, No. (%)	Clonal Isolates, No. (%)	*P* Value
Total	45	31 (68.9)	14 (31.1)	–
Age <65 y	20 (44.4)	15 (48.4)	10 (71.4)	.150
Age ≥65 y	25 (55.6)	16 (51.6)	4 (28.6)	
Sex, male	35 (77.8)	24 (77.4)	11 (78.6)	.931
Sex, female	10 (22.2)	7 (22.6)	3 (21.4)	
Hip joint	17 (37.8)	10 (32.3)	7 (50.0)	.256
Knee joint	28 (62.2)	21 (67.7)	7 (50.0)	
Primary surgery	16 (39.0)	12 (41.4)	4 (33.3)	.631
Revision Surgery	25 (61.0)	17 (58.6)	8 (66.7)	
Native Joint	4 (8.9)	2 (6.4)	2 (14.3)	.393
Prosthetic Joint	41 (9.1)	29 (93.6)	12 (85.7)	
Met MSIS criteria for PJI	33 (64.7)	17 (58.6)	6 (50.0)	.613
Did not meet MSIS criteria for PJI	18 (35.3)	12 (41.4)	6 (50.0)	
Days between prior intervention and positive culture				
<30 (ref)	16 (35.6)	12 (38.7)	4 (28.6)	–
30–119	15 (33.3)	11 (35.5)	4 (28.6)	.916
>120	14 (31.1)	8 (25.8)	6 (42.9)	.305
Prior surgery at an outside hospital				
No	20 (44.4)	14 (45.2)	6 (42.9)	.886
Yes	25 (55.6)	17 (54.8)	8 (57.1)	
No. of surgeries at this hospital prior to positive culture[a]				
0	4 (8.9)	2 (6.4)	2 (14.3)	.418
1 (ref)	24 (53.3)	17 (54.8)	7 (50.0)	–
≥ 2	17 (37.8)	12 (38.7)	5 (35.7)	.986
No. of aspirations at this hospital prior to positive culture[a]				
0	25 (55.6)	17 (54.8)	8 (57.1)	.942
1 (ref)	9 (20.0)	6 (19.4)	3 (21.4)	–
≥ 2	11 (24.4)	8 (25.8)	3 (21.4)	.769
mecA not present	16 (35.6)	11 (35.5)	5 (35.7)	.988
mecA present	29 (64.4)	20 (64.5)	9 (64.3)	
Susceptible to oxacillin	18 (40.0)	12 (38.7)	6 (42.9)	.793
Resistance to oxacillin	27 (60.0)	19 (61.3)	8 (57.1)	

Note. MSIS, Musculoskeletal Infection Society; PJI, prosthetic joint infection.
[a]Refers only to procedures performed on the joint of *Staphylococcus epidermidis* sample collection.

collected in studies measuring host diversity. In addition, we selected only a handful of genes deemed to be important in *S. epidermidis* pathogenicity; it is possible that other genes play a role but were not analyzed. Finally, additional investigation is needed to determine phenotypic resistance patterns associated with *smr* genes and partial *qacA/B* genes in these *S. epidermidis* isolates.

In conclusion, we identified a high degree of antimicrobial resistance genes in *S. epidermidis* isolates from prosthetic and native hip and knee joint cultures. In addition, *S. epidermidis* joint isolates were part of a clonal cluster in 14 (31.1%) of 45 cases. Clusters were generally small (ie, 2–4 patients), separated by months in some cases, and they usually did not meet NHSN criteria for SSI, making detection unlikely in routine clinical and infection prevention practices. As WGS becomes more readily available, it will be a valuable tool in detecting low-level hospital transmission. In this study, clusters appear to be self-limited, demonstrating benefit to universal infection control practices.

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			Novel ST		ST_130				ST_210		ST_218		ST_332				ST_88		
isolate	MLST	Cluster	NEBH-14929	NEBH-17029	NEBH-17829	NEBH-1928	NEBH-24630	NEBH-25330	NEBH-28427	NEBH-3028	NEBH-26128	NEBH-33327	NEBH-9930	NEBH-12230	NEBH-15530	NEBH-19430	NEBH-9028	NEBH-26630	NEBH-25827
NEBH-14929	Novel ST	C1		0															
NEBH-17029		C1																	
NEBH-17829	ST_130					4416	4513	4519											
NEBH-1928							360	366											
NEBH-24630		C2						0											
NEBH-25330		C2																	
NEBH-28427	ST_210	C3								0									
NEBH-3028		C3																	
NEBH-26128	ST_218	C4										2							
NEBH-33327		C4																	
NEBH-9930	ST_332	C5												0	0	0			
NEBH-12230		C5													0	0			
NEBH-15530		C5														0			
NEBH-19430		C5																	
NEBH-9028	ST_88	C6																382	7
NEBH-26630																			379
NEBH-25827		C6																	

Figure 3. Single-nucleotide polymorphism (SNP) distance values for all pairs of samples of matching sequence types (STs). Only samples belonging to STs with >1 sample are shown. Blue cells correspond to pairwise distance of <25 SNPs, indicating clonality between isolates. For samples identified as part of a cluster, they are designated by the cluster number (eg, C2 for cluster 2).

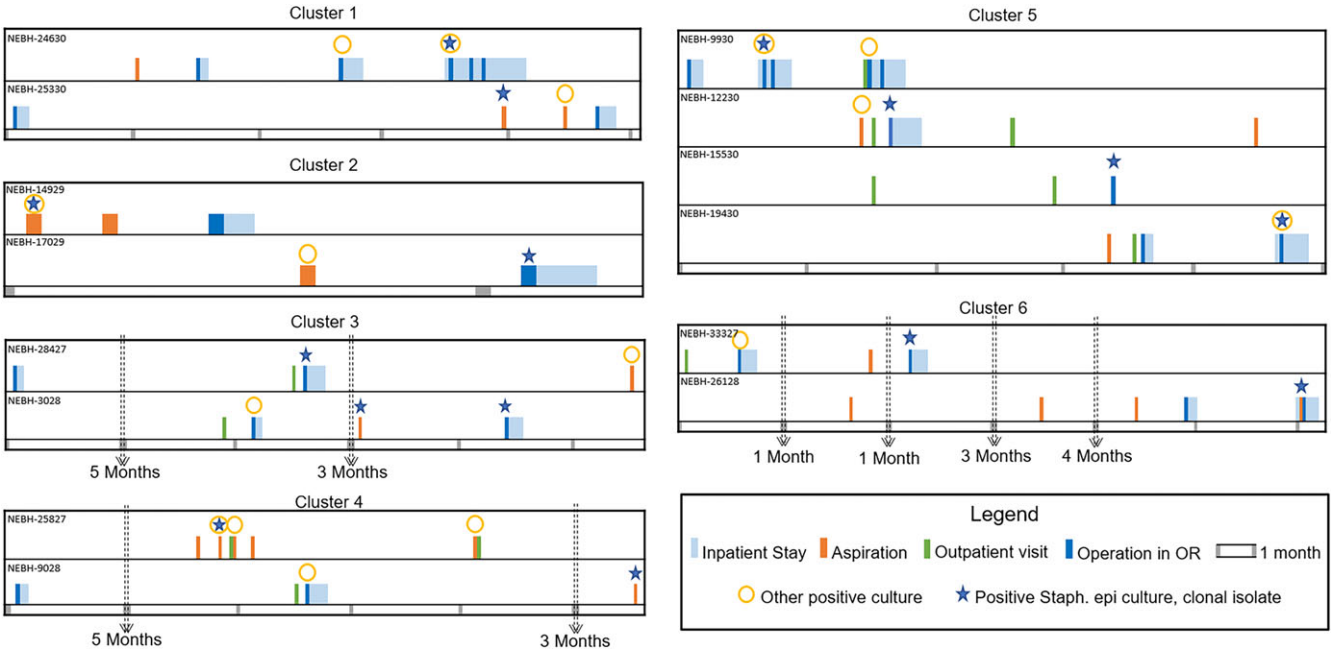

Figure 4. Healthcare visits for patients with clonal *Staphylococcus epidermidis* isolates. Each row represents 1 patient. The bottom row of each cluster's figure shows the time scale by month. Arrows indicate months that are consolidated in the figure. Positive cultures are shown only for the specified joint where the clonal isolate was taken from. Yellow circles indicate another positive culture from the same joint that was not a clonal *Staphylococcus epidermidis* isolate.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2023.253

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Competing interests. Mohamad Sater, Emma Briars, Ian C. Herriott, and Miriam Huntley are Day Zero Diagnostics employees. Both remaining authors report no conflicts of interest relevant to this article.

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