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Original Article

The prevalence of antiseptic tolerance genes among staphylococci and enterococci in a pediatric population

Lauren M. Sommer MS[1], Jennifer L. Krauss PhD[2], Kristina G. Hultén PhD[1], James J. Dunn PhD[2], Sheldon L. Kaplan MD[1] and J. Chase McNeil MD[1]

[1]Department of Pediatrics, Section of Infectious Diseases, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas and [2]Department of Pathology, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas

Abstract

Objective: The *smr* and *qacA/B* genes in *Staphylococcus aureus* confer tolerance to antiseptics and are associated with nosocomial acquisition of infection and underlying medical conditions. Such antiseptic tolerance (AT) genes have also been reported in coagulase-negative staphylococci (CoNS) and enterococci, however, few data are available regarding their prevalence. We sought to describe the frequency of AT genes among bloodstream isolates of *S. aureus*, CoNS and enterococci at Texas Children's Hospital (TCH).

Methods: Banked CoNS, *S. aureus* and enterococci isolated from blood cultures collected bewteen October 1, 2016, and October 1, 2017, were obtained from the TCH clinical microbiology laboratory. All isolates underwent polymerase chain reaction (PCR) assay for the *qacA/B* and *smr* genes. Medical records were reviewed for all cases.

Results: In total, 103 CoNS, 19 *Enterococcus* spp, and 119 *S. aureus* isolates were included in the study, and 80.6% of the CoNS possessed at least 1 AT gene compared to 37% of *S. aureus* and 43.8% of *E. faecalis* isolates ($P < .001$). Among CoNS bloodstream isolates, the presence of either AT gene was strongly associated with nosocomial infection ($P < .001$). The AT genes in *S. aureus* were associated with nosocomial infection ($P = .025$) as well as the diagnosis of central-line–associated bloodstream infection (CLABSI; $P = .04$) and recent hospitalizations ($P < .001$). We found no correlation with genotypic AT in *E. faecalis* and any clinical variable we examined.

Conclusions: Antiseptic tolerance is common among bloodstream staphylococci and *E. faecalis* isolates at TCH. Among CoNS, the presence of AT genes is strongly correlated with nosocomial acquisition of infection, consistent with previous studies in *S. aureus*. These data suggest that the healthcare environment contributes to AT among staphylococci.

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Gram-positive bacteria are the principal causative agents of healthcare-associated infections (HAIs) in both adults and children.[1–3] Chlorhexidine gluconate (CHG)-based antiseptics are commonly employed in efforts to diminish the frequency of HAIs.[4–8] These strategies have been endorsed in guidelines produced by the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America (IDSA) for the prevention of HAIs.[9–11]

A number of efflux pump genes in staphylococci are associated with higher minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) to CHG and other antiseptics (eg, benzalkonium chloride and cetrimide).[12–15] In *S. aureus*, the plasmid-borne *smr* and *qacA/B* gene complexes have been most commonly implicated, with such organisms often being termed antiseptic tolerant (AT).[16] The incidence of AT *S. aureus* has increased following widespread use of CHG in hospital units, and these organisms are also associated with invasive infections.[17–20] In a recent study by our group, the presence of genotypic AT in *S. aureus* was independently associated with chronic medical comorbidities in the host and nosocomial acquisition of infection.[21] The relative prevalence of these genes among *S. aureus* in pediatric populations varies widely, ranging from 1% to 44.5% depending on geographic location and the type of patients studied.[20,22–24] Pediatric-specific data are of relevance given the variable use of CHG in children's hospitals, particularly in neonatal intensive care units (NICUs), arising from concerns for systemic absorption and safety in young children.[25,26] We have reported that among a random sample of *S. aureus* isolates at Texas Children's Hospital (TCH), 32.8% possessed either *smr* or *qacA/B*,[21] suggesting our center represents a high prevalence region for AT.

Other important bacterial contributors to HAIs in children include the coagulase-negative staphylococci (CoNS) and *Enterococcus* spp.[3] CoNS and enterococci can carry *smr* and *qacA/B* and their presence has likewise been associated with elevations in antiseptic MICs.[27–29] However, the current literature regarding the prevalence and clinical significance of AT in these other important gram-positive pathogens is sparse.[30,31] Among a general adult population in Hong Kong, 13.5% of CoNS colonizing isolates were positive for *qacA/B*.[32] The prevalence of AT genes among pediatric clinical isolates of CoNS is limited to a report from

Author for correspondence: J. Chase McNeil, Email: Jm140109@bcm.tmc.edu
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a NICU in France[30] as well as 18 isolates in a study at Seattle Children's Hospital.[31] We sought to determine the frequency of carriage of *smr* and *qacA/B* among bloodstream isolates of CoNS and enterococci compared to that of *S. aureus* at TCH. In addition, we examined the relationship between the presence/absence of these genes and clinical factors in affected patients.

Methods

Microbiology and molecular biology

Blood culture isolates of *S. aureus*, CoNS, and *Enterococcus* spp obtained in the routine course of care from October 1, 2016, to October 1, 2017, were procured from the TCH clinical microbiology laboratory. TCH is a freestanding children's hospital and tertiary-care referral center in Houston, Texas, with 592 licensed inpatient beds and >20,000 admissions annually. All bloodstream isolates identified by the clinical microbiology laboratory are subcultured, frozen at −80°C, and banked for at least 1 calendar year. Isolates for this study were subcultured and transferred to the Edward O Mason, Jr., Infectious Diseases Research Laboratory (IDRL) where they were assigned a strain number and additional analyses were performed. A portion of all isolates immediately underwent whole-DNA extraction using QIAcube (Qiagen, Valencia, CA). For this study, only 1 bacterial isolate per episode of bacteremia was included; no colonization isolates were used in this study. CoNS and enterococci were identified to the species level in the clinical microbiology laboratory using matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy (MALDI-TOF MS, Vitek MS, bioMerieux USA, Durham, NC). Only blood cultures obtained from patients <19 years old were included in this study.

All isolates were subjected to polymerase chain reaction (PCR) assay for the *qacA/B* and *smr* genes using previously published primers.[20] A subset of PCR products from CoNS and *Enterococcus* isolates performed during the first PCR run underwent sequencing, were subjected to basic local alignment search tool (BLAST) algorithms, and were compared against published gene sequences (Genebank JF817385 and JF817387) to confirm the identities of the PCR products. Laboratory personnel performing these studies were blinded to clinical data.

Antimicrobial susceptibility was performed by the TCH clinical microbiology laboratory in the routine course of care using Vitek-2 (bioMerieux USA). In total, 60 CoNS isolates were selected for CHG MIC determinations in the IDRL using the macrobroth dilution method.[20] Every sixth sequential isolate was chosen, and this process was repeated until a total of 60 isolates were selected for MIC determinations.

Corresponding medical records were reviewed for all patients with attention to underlying conditions, preceding CHG use,[21] recent surgery or hospitalization, site of acquisition of infection, and infectious diagnosis. Investigators reviewing medical records and abstracting clinical data were blinded to the results of the molecular analyses, which were performed in tandem with medical record review. The Institutional Review Board of Baylor College of Medicine approved this study.

Infection control practices

Products containing CHG are utilized in a number of infection control practices at our institution.[20] At TCH, CHG is included in central venous line (CVL) insertion and maintenance bundles. Daily CHG baths are employed at TCH for all hospitalized patients with a CVL. All patients undergoing elective surgery at TCH are encouraged to take a CHG bath the night prior to operation, and this agent is the skin cleanser of choice in our operating rooms immediately prior to incision. Additionally, daily CHG mouthwashes are routinely prescribed at TCH for hematopoietic stem cell transplant (HSCT) recipients and those with acute myeloid leukemia (AML). Notable exceptions to these rules include patients cared for in the NICU in which procedural CHG is only used in infants who are (1) at least 28 weeks old (corrected gestational age), (2) at least 7 days old, and (3) weigh at least 1,000 g. Iodophor preparations are used for procedural disinfection in infants not meeting these criteria. CHG baths are only used in infants ≥48 weeks old (corrected gestational age). Quaternary ammonium compound antiseptics are used for the cleaning of rooms and inanimate surfaces at TCH.

Definitions

Sites of acquisition of infection were considered as follows: community-acquired, community-onset healthcare-associated (CO-HCA), and nosocomial. Community-acquired infections were those occurring in otherwise healthy children with onset of signs and symptoms of infection in the community. CO-HCA infections were considered those in which signs and symptoms of infection developed in the outpatient setting in children with underlying medical conditions,[21,33] excluding well-controlled asthma, eczema and allergic rhinitis. This definition was used to capture patients with underlying conditions that place them at higher risk for infection who may not develop infection in the hospital per se. Previous studies in *S. aureus* conducted by our group and others have shown that CO-HCA infections are distinct from community-acquired and hospital-acquired infections in terms of molecular features and antimicrobial susceptibility.[33,34] Nosocomial infections were those in which the patient developed signs/symptoms of infection ≥ 72 hours after hospital admission.[35]

Patients were considered to have had CHG exposure in the prior 3 months if they had documented use of any CHG preparation, surgery or CVL placement at TCH (with the exception of neonates not meeting criteria as specified above) in the preceding 3 months, or diagnosis of AML or HSCT.[21] Patients who underwent surgery but did not have other indications for CHG use were considered to have one-time CHG use; others were considered to have had recurrent CHG use. CLABSI was defined in accordance with national guidelines,[36] and endocarditis was defined using the modified Duke criteria. For purposes of this study, CoNS isolates were regarded as true infections if isolated in >1 blood culture or if considered as a true infection by the treating physician. Length of stay was defined as time in calendar days from date of positive blood culture to hospital discharge. Recurrent infection was considered culture proven recurrence of infection due to an organism of the same species within 30 days of completing treatment.

Statistical analysis

With regard to CoNS infections, only true infections were included in our analyses. Categorical variables were compared using the Fisher exact test and continuous variables were compared using the Wilcoxon rank-sum or Kruskal-Wallis test as appropriate. Two-tailed P values <.05 considered statistically significant. Clinical variables associated with the presence of antiseptic tolerance genes at the $P < .10$ level were included in a multivariable logistic regression analysis. All statistical analyses

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Table 1. General Characteristics of the Study Population

Variable	Total, No. (%)	*S. aureus* (n=119), No. (%)	CoNS (n=103), No. (%)	*Enterococcus* spp (n=19), No. (%)	*P* Value
Median age, years (IQR)	1.3 (0.2–7.9)	3.54 (0.3–11.5)	0.91 (0.16–7.9)	0.9 (0.12–5.8)	.01
Age ≤28 d	31 (12.9)	13 (10.9)	14 (13.5)	4 (21.1)	.40
Female gender	105 (43.5)	49 (41.2)	47 (45.6)	9 (47.4)	.76
Black race	45 (18.6)	20 (16.8)	22 (21.3)	3 (15.8)	.67
Hispanic ethnicity	102 (42.3)	50 (42)	44 (42.7)	8 (42.1)	1
Underlying medical conditions[a]	189 (78.4)	77 (64.7)	101 (98.1)	11 (57.8)	<.001
Prematurity	43 (17.8)	17 (14.3)	24 (23.3)	2 (10.5)	.17
Malignancy	48 (19.9)	12 (10.1)	35 (33.9)	1 (5.3)	<.001
Congenital heart disease	30 (12.4)	18 (15.1)	12 (11.6)	0	.19
Neurologic conditions	9 (3.7)	3 (2.5)	2 (1.9)	4 (21.1)	.005
Short gut	26 (10.7)	10 (8.4)	14 (13.6)	2 (10.5)	.45
Solid organ transplant	8 (3.3)	2 (1.7)	6 (5.8)	0	.20
End-stage renal disease	4 (1.7)	2 (1.7)	2 (1.9)	0	1
Acquisition					<.001
Community acquired	57 (23.6)	48 (40.3)	0	9 (47.4)	
Community-onset healthcare associated	95 (39.4)	33 (27.7)	57 (55.3)	5 (26.3)	
Nosocomial	89 (36.9)	38 (31.9)	46 (44.6)	5 (26.3)	
Source of bacteremia					<.001
CLABSI	105 (43.6)	28 (23.5)	74 (71.8)	3 (15.7)	
Endocarditis	21 (8.7)	16 (13.4)	4 (3.9)	1 (5.3)	
Musculoskeletal infection	36(14.9)	36 (30.2)	0	0	
Skin and soft-tissue infection	12 (5)	11 (9.2)	1 (0.9)	0	
Surgical site infection	6 (2.5)	5 (4.2)	1 (0.9)	0	
Urinary tract infection	3 (1.2)	0	1 (0.9)	2 (10.5)	
Bacteremia without a focus	41 (17)	13 (10.9)	16 (15.5)	12 (63.1)	
Other	18 (7.5)	10 (8.4)	7 (6.7)	1 (5.3)	

Note. IQR, interquartile range; CLABSI, central-line–associated bloodstream infection.
[a]Most common underlying conditions listed, categories are not mutually exclusive.

were performed with Stata version 15 software (Stata Corp, College Station, TX).

Results

During the study period, 404 viable isolates were obtained from 389 unique patients. Moreover, 254 patients with blood cultures positive for CoNS had complete medical records and 151 of these were considered to be contaminants. After excluding these contaminants, 103 CoNS, 119 *S. aureus*, and 19 *Enterococcus* isolates (totaling 241 unique isolates from 238 patients) were included in final analyses. The median age of studied patients was 1.3 years (interquartile range [IQR], 0.2–7.9 years), and 78.4% of patients had underlying medical conditions (Table 1). Significant differences in age, comorbidities, and diagnoses existed between patients with bacteremia due to CoNS, *S. aureus*, and enterococci.

7 different CoNS species were identified by MALDI-TOF MS: *S. epidermidis* (n = 70), *S. hominis* (n = 22), *S. haemolyticus* (n = 4), *S. capitis* (n = 3), *S. warnerii* (n = 2), *S. lugdenensis* (n = 1), and *S. saprophyticus* (n = 1). Most enterococci were *E. faecalis* (n = 16, 84.2%) with the remainder being *E. faecium* (n = 3). Among *S. aureus* isolates, 25 of 119 (21%) were methicillin resistant.

Antiseptic tolerance genes

Overall, 83 of 103 CoNS isolates (80.6%) possessed either *qacA/B* or *smr* compared to 44 of 119 of *S. aureus* isolates (37%) and 7 of 16 *E. faecalis* isolates (43.8%) and none of 3 *E. faecium* isolates ($P < .001$) (Fig. 1). The *qacA/B* gene was detected in 16 of 119 *S. aureus isolates* (13.4%), 73 of 103 CoNS isolates (70.8%), and 7 of 16 of *E. faecalis* isolates (43.8%; $P < .001$). The *smr* gene was detected in 28 of 119 *S. aureus* isolates (23.5%), 34 of 103 CoNS isolates (33%), and 4 of 16 *E. faecalis isolates* (25%; $P = .28$). Both AT genes were detected in 24 of 103 CoNS isolates (23.3%), 4 of 16 *E. faecalis* isolates (25%), and none of the *S. aureus* isolates ($P < .001$). The proportion of CoNS isolates with AT genes was similar among isolates considered true infections (83 of 103, 80.6%) and contaminants (128 of 151, 84.7%; $P = .39$). Sequenced *qacA/B*- and *smr*-PCR products obtained

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Table 2. Comparison of Patients with Bacteremia Due to *qacA/B*-Positive Versus *qacA/B*-Negative CoNS

Variable	*qacA/B*-Positive CoNS (n=73), No. (%)	*qacA/B*-Negative CoNS (n=30), No. (%)	*P* Value
Median age, y (IQR)	1.4 (0.23–9.4)	0.5 (0.08–6.4)	.32
Age ≤ 28 d	9 (12.3)	5 (16.7)	.54
Median duration of bacteremia, d (IQR)	1 (1–2)	1 (1–2)	.65
CLABSI	53 (72.6)	21 (70)	1
Line removed	24/53 (45.3)	11/21 (52.4)	.62
CHG use in prior 3 mo	57 (78.1)	22 (73.3)	.62
1 CHG use	6 (8.2)	2 (6.6)	1
Recurrent CHG use	51 (69.9)	20 (66.6)	.86
CVL in situ	63 (86.3)	28 (93.3)	.5
Hospital admission in prior 3 mo	69 (94.5)	29 (96.7)	1
Surgery in prior 3 mo	53 (72.6)	21 (70)	.8
Underlying conditions	71 (97.3)	30 (100)	1
Nosocomial acquisition of infection[a]	41 (56.1)	5 (16.7)	<.001
Antibiotics in prior 3 mo	68 (93.1)	27 (90)	.69
Infection recurrence	1 (1.4)	2 (6.7)	.20
Mortality	1 (1.4)	1 (3.3)	.50
Median length of stay, d (IQR)	9 (4–33.5)	8 (5–3)	.92

Note. IQR, interquartile range; CLABSI, central-line–associated bloodstream infection; CHG, chlorhexidine gluconate; CVL, central venous line.
[a]No patients with CoNS bacteremia had a community-acquired infection.

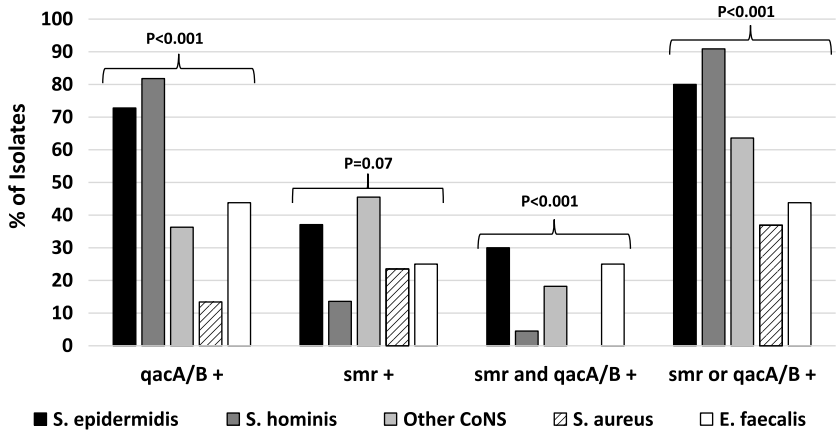

Fig. 1. Comparison of proportion of isolates with antiseptic tolerance genes in staphylococci and enterococci (n = 241). Simple proportions of isolates bearing genes of interest were compared using the Fisher exact test.

from CoNS and *E. faecalis* were identical to published sequences of these respective genes in *S. aureus*.

Antiseptic tolerance

In total, 60 CoNS isolates had CHG MICs, as determined by broth dilution. Isolates with both *qacA/B* and *smr* had higher MICs than those without these genes (MIC_{90}, 0.25 vs 0.03 μg/mL; $P = .06$) (Supplemental Table 1).

Antiseptic tolerance and clinical variables

Among patients with CoNS infections, a greater proportion of *qacA/B*-positive strains were associated with nosocomial infections than *qacA/B*-negative isolates (41 of 73 [56.1%] vs 5 of 30 [16.7%]; $P < .001$) (Table 2). The *smr*-positive CoNS infections were more often associated with nosocomial acquisition (21 of 34 [61.8%] vs 25 of 69 [36.2%] $P = .02$) and a longer median length of hospital stay (14.5 vs 6.5 days; $P = .02$) (Table 3). When considered as a group, antiseptic tolerant CoNS were associated with a higher rate of nosocomial acquisition of infection (46 of 83 [55.4%] vs 0 of 20; $P < .001$) (Supplemental Table 2). We observed no differences in any other examined clinical variable between antiseptic-tolerant and -susceptible CoNS.

Antiseptic-tolerant and -susceptible *S. aureus* were also compared (Table 4). Patients with AT *S. aureus* infections were younger, had more medical comorbidities, more recent hospitalizations, and more exposure to CHG and antibiotics. They more often acquired infection in the hospital and more often

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Table 3. Comparison of Patients with Bacteremia Due to *smr*-Positive Versus *smr*-Negative CoNS

Variable	*smr*-Positive CoNS (n=34), No. (%)	*smr*-Negative CoNS (n=69), No. (%)	*P* Value
Median age, y (IQR)	0.69 (0.13–8.8)	1.24 (0.23–6.24)	.99
Age ≤ 28 d	5 (14.7)	9 (13)	1
Median duration of bacteremia, d (IQR)	1 (1–2)	1 (1–2)	.39
CLABSI	24 (70.6)	50 (72.4)	1
Line removed	11/24 (45.8)	24/50 (48)	1
CHG use in prior 3 mo	27 (79.4)	52 (75.3)	.81
1 CHG use	7 (20.5)	1 (1.4)	.002
Recurrent CHG use	20 (58.8)	51 (73.9)	.17
CVL in situ	29 (85.3)	62 (89.8)	.53
Hospital admission in prior 3 mo	32 (94.1)	66 (95.6)	1
Surgery in prior 3 mo	25 (73.5)	49 (71)	1
Underlying conditions	33 (97.1)	68 (98.5)	1
Nosocomial acquisition of infection[a]	21 (61.8)	25 (36.2)	.02
Antibiotics in prior 3 mo	31 (91.2)	64 (92.7)	1
Infection recurrence	0	3 (4.3)	.55
Mortality	0	2 (2.9)	1
Median length of stay, d (IQR)	14.5 (7–54)	6.5 (3–19.5)	.02

Note. IQR, interquartile range; CLABSI, central-line–associated bloodstream infection; CHG, chlorhexidine gluconate; CVL, central venous line.
[a]No patients with CoNS bacteremia had a community-acquired infection.

experienced infection recurrence. Additionally, AT *S. aureus* isolates were more often associated with a diagnosis of CLABSI (15 of 44 [34.1%] vs 13 of 75 [17.3%]; $P = .046$) and less often with the diagnosis of musculoskeletal infection (2 of 44 [4.5%] vs 34 of 75 [45.3%]; $P < .001$) than antiseptic susceptible infections. In multivariable analyses, nosocomial/CO-HCA infections were more often associated with AT in *S. aureus*, whereas musculoskeletal infections were less often associated with AT. Among enterococci, there was no significant association with AT genes and any examined clinical variable.

Discussion

Despite advances in infection control and prevention, HAIs still cause substantial morbidity in both adults and children, and *S. aureus*, CoNS, and enterococci are significant contributors.[3] Antiseptics have been demonstrated to be an effective means to reduce the incidence of HAIs; however, with widespread use of these agents, concerns have been raised in recent years regarding the emergence of reduced susceptibility.

We investigated the prevalence of AT genes among staphylococci and enterococci causing bacteremia at a large children's hospital. Previous studies in CoNS have reported that 13%–80% of isolates possessed AT genes.[27,30–32] We found that 80.6% of CoNS isolates possessed either *qacA/B* or *smr*. The proportion of isolates with AT in our study is higher than that reported at most other institutions, particularly those centers caring for children. Soma et al[31] reported that 65% of 18 CoNS isolates recovered from skin swabs studied at Seattle Children's Hospital bore *qacA/B*. A similar proportion of CoNS were positive for *qacA/B* among a study of CLABSI isolates obtained from very-low-birth-weight infants in France.[30] The high frequency of *qacA/B*-positive CoNS in our population is comparable to a study from the United Kingdom in which 80% of bloodstream *S. epidermidis* isolates carried *qacA/B*.[27] In our center, the frequency of detection of AT genes in CoNS was much higher than that detected among *S. aureus* (36.2%). Notably, however, the proportion of *S. aureus* isolates positive for AT genes was higher than that reported by other studies in pediatric populations (1%–18.5%)[22–24] but was consistent with prior research at our institution.[21,22]

In previous studies of *S. aureus* conducted at our institution, the presence of AT genes was independently associated with nosocomial infections and underlying medical conditions in the host.[21] In the present study, AT *S. aureus* were again associated with underlying medical conditions and nosocomial acquisition of infection as well as a number of other clinical factors in univariable analyses including recent hospitalization and the diagnosis of CLA-BSI. Importantly, we noted a statistically significant association with the presence of genotypic AT in CoNS and nosocomial acquisition of infection. These findings suggest that the healthcare environment and/or medical complexity select for AT in other organisms in addition to *S. aureus*. This is of particular importance given that previous studies examining the epidemiology and clinical impact of AT have largely focused on *S. aureus* with little attention given to other pathogens. CoNS was the predominant cause of all pediatric HAIs in a multinational study,[37] highlighting the clinical significance of this pathogen. We found no other clinical variables to be associated with AT in CoNS; the small number of healthy patients with true CoNS infections likely limited the degree to which other clinical factors could be associated with AT in these organisms. In contrast to our findings in staphylococci, we observed no relationship between AT genes in enterococci and any examined clinical variable; this was likely a consequence of the small number of enterococci studied.

We have previously reported an association with AT in *S. aureus* and invasive infections as well as prolonged hospital stay.[21] In the present study, we found an association with genotypic AT in *S.*

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Table 4. Comparison of Patients With Bacteremia Due to Antiseptic-Tolerant Versus -Susceptible *S. aureus*

Variable	Antiseptic Tolerant *S. aureus* (n=44), No. (%)	Antiseptic Susceptible *S. aureus*, (n=75), No. (%)	*P* Value	Adjusted *P* Value	OR	95% CI
Median Age, y (IQR)	0.74 (0.13–8.3)	6.3 (1.1–12.6)	.008	0.22[a]	1.97	0.66–5.87
Age ≤ 28 d	8 (18.2)	5 (6.7)	.07			
Median duration of bacteremia, d (IQR)	1 (1–2)	1 (1–2)	.67			
CLABSI	15 (34.1)	13 (17.3)	.046	.88	0.9	0.24–3.34
Line removal	10 (66.7)	10 (76.9)	.69			
Musculoskeletal infection	1 (2.3)	31 (41.3)	<.001	.03	0.15	0.03–0.84
CHG use in prior 3 mo	24 (54.5)	25 (33.3)	.034	.54	1.6	0.36–7.03
1 CHG use	11 (24)	11 (14.6)	.22			
Recurrent CHG use	13 (29.5)	14 (18.6)	.18			
CVL in situ	25 (56.8)	21 (28)	.003	.89	1.1	0.27–4.35
Hospital admission in prior 3 mo	37 (84.1)	36 (48)	<.001	.62	0.56	0.06–5.53
Surgery in prior 3 mo	23 (52.3)	26 (34.6)	.08	.22	0.37	0.08–1.78
Underlying conditions	39 (88.6)	38 (51.3)	<.001	.9	1.1	0.19–6.48
Acquisition			<.001	.049[b]	3.3	1.5–21.1
Community acquired	7 (15.9)	41 (54.6)				
Community-onset healthcare associated	17 (38.6)	16 (21.3)				
Nosocomial	20 (45.5)	18 (24)				
Antibiotics in prior 3 mo	39 (88.6)	39 (52)	<.001	0.25	2.94	0.47–18.24
Recurrent infection[c]	8 (18.2)	2 (2.6)	.005			
Mortality	2 (4.5)	2 (2.6)	.63			
Median length of stay, d (IQR)	14 (6–84)	10 (6–35)	.19			
Methicillin resistant	13 (29.5)	12 (16.2)	.11			
Clindamycin resistant	13 (30.2)	13 (17.6)	.17			

Note. OR, odds ratio; CI, confidence interval; IQR, interquartile range; CLABSI, central-line–associated bloodstream infection; CHG, chlorhexidine gluconate; CVL, central venous line.
[a]In multivariable analyses, age was dichotomized as > vs ≤ 0.33 years (the bottom quartile of age for all patients with *S. aureus* bacteremia).
[b]Acquisition of infection is dichotomized as healthcare associated (CO-HCA and nosocomial) vs community-acquired.
[c]3 patients with antiseptic-tolerant *S. aureus* and infection recurrence had CLABSI initially treated with CVL in situ compared to 1 patient in the antiseptic-susceptible group with infection recurrence. If these 4 patients are removed from the analyses, a statistically significant relationship between antiseptic tolerance and infection recurrence remains (5/41 [12.2%] vs 1/74 [1.4%]; $P = .03$).

aureus and recurrence of infection; however, the reasons for this observation are unclear. Studies using ex vivo and in vivo models suggest that *S. aureus* expressing such multidrug-resistance efflux pumps may have an enhanced ability to colonize surfaces as well as cause disease.[38,39] Possibly, if such organisms have an enhanced colonization capacity, they may be more likely to cause recurrent infection despite appropriate treatment. This finding is, in part, also likely related to the higher rate of CLA-BSI in the tolerant group and recurrences occurring as a result of not removing infected central lines in a minority of cases. Also, this phenomenon might be a consequence of virulent strain types that happen to possess AT genes rather than a consequence of the genes themselves. Such findings further highlight the potential impact of AT strains for public health. Notably, however, the finding of higher recurrence in AT *S. aureus* infections may have been a result of these patients having a greater degree of medical complexity and thus being more likely to fail treatment.

Additional limitations to this study should be acknowledged. Foremost, these findings are from a single center with a previously described high prevalence of AT *S. aureus*[20,21]; thus, our findings may not be generalizable to all regions. The retrospective nature of the study limits the degree to which clinical risk factors can be definitively associated with AT organisms. Additionally, given that colonization cultures were not examined in this study, we are unable to assess the impact of AT organism colonization on risk of subsequent bacteremia or the potential mitigating effects of antibiotic/antiseptic use.

In conclusion, genotypic AT is common among bloodstream staphylococci and *E. faecalis* isolates at our institution. The presence of AT genes was strongly associated with nosocomial acquisition of infection in staphylococci, implying a role for the hospital environment in selecting for these pathogens. Larger studies are needed to further explore and validate these findings.

Author ORCIDs. J. Chase McNeil, http://orcid.org/0000-0002-0232-7491

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Conflicts of interest. Dr Kaplan serves as the primary investigator (PI) on an investigator-initiated clinical trial sponsored by Allergan as well as the site PI of a clinical trial sponsored by Merck. Dr McNeil serves as a co-investigator on these studies, neither of which is directly related to the present work. No authors have significant financial conflicts of interest.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2019.3

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