Risk Factors and Outcomes Associated With Hospital-Onset Peripheral Intravenous Catheter–Associated \textit{Staphylococcus aureus} Bacteremia

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\textbf{Background.} Peripheral venous catheters (PVCs) are common in hospitals, but the literature surrounding PVC-associated bacteremia is lacking. We describe incidence rates, risk factors, and outcomes related to PVC-associated \textit{Staphylococcus aureus} bacteremia (SAB), a common cause of hospital-onset (HO) SAB.

\textbf{Methods.} This is a retrospective case–control study conducted at a 537-bed teaching community hospital during 2015–2016. Cases were adult inpatients with HO SAB with infectious diseases documentation of the PVC as the only source of bacteremia. Cases were matched 1:2 with controls on approximate PVC insertion date, age, mortality prediction score, and insurance type. Odds ratios (ORs) were estimated using conditional logistic regression. PVC utilization was estimated by a point-prevalence survey from July 2017.

\textbf{Results.} Of 205 SAB episodes, 160 were community-onset and 45 were HO; 16 (36%) HO cases were PVC-associated. Cases (n = 16) were more likely than controls (n = 32) to have a PVC placed in the antecubital area (odds ratio [OR], 11.9; 95\% confidence interval [CI], 1.5–95.7; \(P = .02\)) and PVC duration \(\geq 4\) days (OR, 4.0; 95\% CI, 1.1–15.2; \(P = .04\)). The point prevalence of at least 1 PVC in adult inpatients was 86\%, and the incidence density of HO PVC–associated SAB was 0.15 per 1000 PVC-days. The mean length of stay for cases was 13.2 days. All cases successfully completed parenteral antibiotics with a mean treatment length of 23.6 days.

\textbf{Conclusions.} PVC-associated SAB is a common cause of HO SAB that results in significant morbidity. PVC placement in the antecubital area and line duration should be minimized to reduce HO SAB.

\textbf{Keywords.} Bacteremia; hospital-onset; peripheral venous catheter; phlebitis; \textit{Staphylococcus aureus}.

Approximately 80\% of hospitalized patients in the United States have 1 or more intravenous catheters placed during the course of their hospital stay [1–3]. Although intravenous catheters are common in hospitals, they are associated with increased risk of bacteremia, which can prolong length of hospital stay and increase health care costs by an estimated \$20,000–30,000 per episode of bacteremia [3–5].

Peripheral venous catheter (PVC)–associated bacteremia occurs in approximately 0.18\% of patients [3, 6–8]. Worldwide, an estimated 1 billion or more PVCs are inserted in hospitalized patients each year [9]. Although the rate of bacteremia is lower in patients with PVCs than central venous catheters (CVCs), the sheer number of PVCs in use indicates that a large number of patients are at risk for infection [4, 10]. Unlike central line–associated bloodstream infections (CLABSIs), episodes of PVC-associated bacteremia are not reportable to the Centers for Disease Control and Prevention and thus are not used as a pay-for-performance measure by the Centers for Medicare & Medicaid Services [11]. There is less research on these types of infections when compared with CLABSIs.

\textit{Staphylococcus aureus} causes the majority of PVC-related bloodstream infections. Among \textit{S. aureus} bloodstream infections, PVCs are identified as the source 4\%–35\% of the time and are one of the most common causes of hospital-onset (HO) \textit{S. aureus} bacteremia (SAB) [3, 7, 8, 12–19]. Given the relative paucity of data surrounding PVC-associated SAB, we aimed to describe the incidence rates, modifiable risk factors, and outcomes related to HO PVC–associated SAB.

\textbf{METHODS}

\textbf{Study Design and Population} We conducted a retrospective case–control study of HO SAB episodes among adult inpatients (age \(> 18\) years) between January 1, 2015, and December 31, 2016, at Saint Joseph Mercy Hospital in Ann Arbor, Michigan, a 537-bed, non-university-affiliated, community teaching hospital. Cases of HO SAB
were defined as a positive blood culture occurring on or after day 3 of admission, with the date of admission considered day 1. This study was approved by the hospital’s institutional review board.

Prevalence and Incidence
We conducted a point-prevalence survey of all adult inpatients (except the mother/baby and psychiatric units) in July 2017 to estimate the proportion of inpatients with ≥1 PVCs. Hospital administrative data were used to derive the total number of inpatient days during the study period. We calculated the approximate number of PVC days during the study period and used these to estimate the incidence rate for HO SAB during the study period per 1000 PVC days. Through the point-prevalence survey, the anatomic location of PVC placement was determined based on nursing documentation.

Case and Control Definitions
Cases were defined as patients with a first HO episode of bacteremia with a blood culture positive for S. aureus, documentation by the consulting infectious diseases physician that the PVC was the source of bacteremia (infectious phlebitis documented at the PVC site including palpable cord and/or exudate), and no other source of bacteremia determined by medical record review through adjudication by an infection preventionist and 2 infectious disease physicians. Sources of bacteremia listing >1 possible source or unclear source were defined as unknown. Recurrent episodes of SAB that were attributed to the same source in the same patient, but on multiple hospitalizations, were excluded.

Controls were selected from those who had a PVC in place during a portion of their inpatient visit. We excluded patients from the mother/baby and psychiatric units. Each case of HO PVC–associated SAB was matched to 2 controls with PVCs based on PVC insertion date (±3 days), age (±5 years), an internal predicted risk of mortality (PRISM) score [20], and insurance type (no insurance, Medicare, Medicaid, or commercial insurance). Patients who died within 2 days of PVC placement were excluded from the control selection. Two controls per case were randomly selected through computer-generated random digits from the group of eligible controls.

Variable Definitions
We reviewed electronic medical records for patient demographic characteristics, underlying medical history, and characteristics associated with PVCs. A description of the number of insertion attempts is presented. However, this variable was not included in bivariate or multivariate analyses because documentation was missing for a large proportion of the study population. Duration of PVC placement is presented as a dichotomous variable. The dichotomy of 4 days was utilized based on previous recommendations from the Centers for Disease Control and Prevention (CDC) to change PVCs every 72–96 hours [2].

Statistical Analysis
We described demographic and clinical characteristics using simple descriptive statistics such as mean (SD) and number (percentage). Conditional logistic regression was used to estimate the odds ratio (OR), 95% confidence interval (CI), and P value between exposure of PVC and outcome of HO SAB in a univariate and multivariate fashion. All statistical tests were 2-sided, and a P value <.05 was considered statistically significant. Given the exploratory nature of the study, we decided a priori not to adjust the P value for multiple testing.

RESULTS
Study Population
There were 214 episodes of SAB between January 2015 and December 2016. Of these, 2 occurred in pediatric patients and were excluded. Another 7 episodes were excluded because they were a recurrent episode of bacteremia in which the same source was attributed as the cause of infection in each episode. Of the remaining 205 episodes of SAB, 45 were defined as being HO, and 160 were community-onset. The sources of all the bacteremia episodes are presented in Table 1. There were 16 HO SAB episodes (12 methicillin-susceptible S. aureus and 4

| Source             | Total S. aureus Bacteremia (n = 205), No. (%) | Hospital-Onset S. aureus Bacteremia (n = 45), No. (%) | Community-Onset S. aureus Bacteremia (n = 160), No. (%) |
|--------------------|---------------------------------------------|---------------------------------------------------|-----------------------------------------------------|
| Soft tissue/bone   | 67 (32.7)                                   | 4 (8.9)                                           | 63 (39.4)                                           |
| PVC                | 18 (8.8)                                    | 16 (35.6)                                         | 2 (1.3)                                             |
| CVC or PICC        | 14 (6.8)                                    | 7 (15.6)                                          | 7 (4.4)                                             |
| Hemodialysis       | 13 (6.3)                                    | 2 (4.4)                                           | 11 (6.9)                                            |
| Pulmonary          | 8 (3.9)                                     | 0 (0.0)                                           | 8 (5.0)                                             |
| Endovascular       | 7 (3.4)                                     | 1 (2.2)                                           | 6 (3.8)                                             |
| Biliary            | 1 (0.5)                                     | 0 (0.0)                                           | 1 (0.6)                                             |
| Urinary            | 3 (1.5)                                     | 0 (0.0)                                           | 3 (1.9)                                             |
| Unknown            | 74 (36.1)                                   | 15 (33.3)                                         | 59 (36.9)                                           |

Abbreviations: CVC, central intravenous catheter; PICC, peripherally inserted central catheter; PVC, peripheral intravenous catheter.
methicillin-resistant *S. aureus*) that were associated with a PVC (Figure 1).

**Prevalence and Incidence**
During the study period, there were 123,604 patient-days. A point-prevalence survey found 276 of 320 (86%) adult inpatients had at least 1 PVC, with 51.3% of PVCs in the arm, 27.6% in the antecubital area, and 20.8% in the hand or wrist. We used these results to estimate the number of PVC days during the study period ($0.86 \times 123,604 = 106,299$ PVC-days). The estimated incidence density of PVC-related HO SAB was 0.15 per 1000 PVC-days.

**Identification of Risk Factors**
Cases and controls were similar with respect to most demographic and underlying medical comorbidities (Table 2). However, cases were almost 12 times as likely to have PVCs placed in the antecubital area vs all other placement locations (odds ratio [OR], 11.9; 95% confidence interval [CI], 1.5–95.7; *P* = .02), 4 times more likely than controls to have a PVC duration of ≥4 days (OR, 4.0; 95% CI, 1.1–15.2; *P* = .04), 2.6 times more likely to have PVC placement in the field or emergency department vs in an inpatient unit or the operating room (OR, 2.6; 95% CI, 0.7–9.1; *P* = .15), and 2.3 times more likely to be male (OR, 2.3; 95% CI, 0.7–8.1; *P* = .18). Additionally, the mean length of stay for cases was 13.2 days (SD, 3.8 days; range, 8–23 days) vs 5 days (SD, 4.8 days; range, 1–24 days) for controls.

We evaluated the interaction between anatomical PVC placement and line duration using a logistic regression model (Table 3). Results showed that a patient with antecubital PVC placement and a line duration of ≥4 days was 50.4 times (95% CI, 2.4–1043.8; *P* = .01) more likely to have PVC-associated HO SAB than a patient without antecubital PVC placement and a line duration of less than 4 days. A patient with antecubital PVC placement and a line duration of <4 days was 12.6 times (95% CI, 1.3–117.5; *P* = .03) more likely to have PVC-associated HO SAB than a patient without antecubital PVC placement and a line duration of less than 4 days.

**Characteristics of S. aureus Bacteremia Cases**
All 16 case patients were seen by an infectious diseases physician and received parenteral antibiotics; the 12 patients with MSSA infections were treated with cefazolin, whereas 2 patients with a MRSA infection were treated with vancomycin and 2 were treated with daptomycin. The mean length of treatment was 23.6 days (SD, 11.1 days; range, 14–42 days). All case patients had an echocardiogram; 5 (31.3%) had a transthoracic echocardiogram (TTE), 5 (31.3%) had a transesophageal echocardiogram (TEE), and 6 (37.4%) had both a TTE and a TEE. Eleven (69%) of the case patients had a thrombus identified on ultrasound near the PVC insertion site, 1 (6%) had endocarditis, and 2 (13%) had metastatic spread to other sites, including septic emboli to the lungs and septic arthritis of the shoulder. No case patients died within 30 days of their hospital stay.
In this case–control study conducted between January 2015 and December 2016, we report a number of important findings. First, PVC-associated SAB was the most common cause of HO SAB, representing 36% of all episodes, whereas it rarely caused community-onset SAB (1%). Second, PVCs placed in the antecubital area and PVCs with durations of ≥4 days were significantly more likely to be associated with HO PVC–associated SAB.

We find, as have others, that PVC-associated SAB is both an under-recognized and common cause of HO SAB [7, 8, 12–16]. The finding that antecubital PVC placement was...
associated with PVC-associated SAB is consistent with previous studies. A recent experience from a tertiary care center of PVC-associated SAB found 27 cases of thrombophlebitis associated with SAB that occurred in an old site where the PVC had already been removed [7]. A majority of these infections (16/27, 59%) were related to a PVC site in the proximal upper extremity (proximal forearm and antecubital fossa) [7]. Another retrospective study of 24 cases of PVC-associated SAB in adult patients found that the PVC was placed in the antecubital area in 67% of patients with PVC-associated SAB [12].

It is likely that the risk associated with placement of PVC in the antecubital area and SAB is related to the skin microbiome of the antecubital area. The antecubital fossa has more *Staphylococcus* species than other areas of the upper and lower arms [21, 22]. Bacteremia arises from colonization of the external surface of catheters and migration of the bacteria down the PVC and into the bloodstream [23]. Additionally, the antecubital area, being a point of flexion, may cause trauma to the PVC insertion site, allowing bacteria to colonize the external surface of the catheter more frequently. When bacteria are present in high densities, as they are in the antecubital area, colonization is much more likely [23].

Our finding that duration of PVCs for ≥4 days is associated with HO PVC–associated SAB differs from recent literature findings and policy changes by the CDC. Previously, it was recommended that all PVCs be replaced routinely every 72–96 hours to reduce the risk of phlebitis and bacteremia [2]. A recent systematic review also concluded that dwell times of PVCs beyond 3 days increase the risk of PVC colonization and, thereby, the risk of PVC-associated bacteremia [8]. However, there have been several studies that specifically recommended PVC replacement upon clinical indication vs routine replacement every 72–96 hours [2, 24–29]. A review of 7 randomized controlled trials that compared routine removal of PVCs with removal of PVCs only when clinically indicated found no evidence to support changing catheters every 72 to 96 hours and recommended that hospitals should consider modifying PVC policies to changing devices only when clinically indicated [2]. However, this review only included 3 cases of PVC-associated bacteremia. Recommendations from the CDC state that there is no need to replace PVCs more frequently than every 72–96 hours in adults, but leave replacement of PVCs when clinically indicated as an unresolved issue [30]. Replacement upon clinical indication allows the opportunity for the duration of PVCs to be longer, which our study, similar to others, shows is a risk factor for HO PVC–associated SAB [3, 12, 17, 19]. Many hospitals, including our own, have transitioned to PVC replacement upon clinical indication.

Clinical setting of PVC placement and sex may be associated with HO PVC–associated SAB. However, these estimates are uncertain, with wide confidence intervals, and cannot be investigated further in this study. Other studies, however, have found an association between the department in which the PVC was placed and SAB [3, 17, 23, 31]. A prospective study of all health care–associated SAB episodes found that >60% of all PVC-associated SAB episodes were related to a PVC that was placed in the emergency department or by the ambulance service [3]. Lines placed before inpatient admission have been associated with higher infection rates—likely associated with less strict adherence to aseptic techniques [23]. One study implemented several key measures to reduce the risk of SAB during an intervention period, which included a flagging alert sticker indicating that PVCs placed outside the hospital would require removal within 24 hours. The study found that the rate of PVC-associated SAB was 63% lower during the intervention period compared with the baseline period [19]. Further, a retrospective cohort study of 570 adult patients with a PVC placed in the emergency department found that approximately half were never used [31]. As placement of PVCs before the inpatient setting has been associated with SAB, and these lines are often placed and never used, emergency department policies should investigate the recommendation to place PVCs only when medically necessary.

Although not statistically significant, the association between males and SAB is intriguing. A study on the microbiome of humans found that many host factors, including sex, can alter the microbiome of the skin [21, 22]. Additionally, there are physiological and anatomical differences such as sweat, sebum, and hormone production that partially explain the microbial differences on the skin between males and females [21].

### Table 3. Evaluation of Interaction Between Antecubital PVC Placement and Line Duration for Hospital-Onset PVC-Associated *Staphylococcus aureus* Bacteremia Using Logistic Regression

| Anatomic Placement | Line Duration | Odds Ratios (95% Confidence Interval) |
|--------------------|---------------|---------------------------------------|
| Model (standard error) | 2.5315 (1.1) | 1.3876 (0.8) | - |
| Antecubital | <4 d | 12.6 (1.3–1175) |
| Nonantecubital | ≥4 d | 4.0 (0.8–20.6) |
| Antecubital | ≥4 d | 50.4 (2.4–1043.8) |
| Reference | Nonantecubital | <4 d | 1.0 |

Abbreviation: PVC, peripheral intravenous catheter.

*N = 16 cases and 32 controls.*
We found an incidence density of 0.15 HO PVC–related SAB episodes per 1000 PVC-days, which is more than twice the 0.07/1000 PVC-days reported in a retrospective study of 544 cases of SAB [12]. Although the rate of PVC-associated SAB is low, the prevalence of PVCs used in the inpatient population is high enough to warrant strict adherence to insertion and maintenance best practice by clinical teams, with an emphasis that providers maintain appropriate clinical suspicion to recognize and diagnose PVC-associated SAB.

There are several limitations to our study. Given the retrospective nature, we were unable to investigate the frequency of PVC access and ongoing PVC necessity or observe adherence to insertion and maintenance protocols. A single point-prevalence survey was used to estimate the total number of PVC-days during the study period. The mean of several point-prevalence surveys would increase the reliability of these estimates. This study was a single-center experience resulting in a small sample size. Despite these limitations, our results are consistent with previous studies that show that placement of PVCs in the antecubital area and prolonged PVC duration are associated with HO SAB [3, 7, 12, 17, 19]. Avoiding placement of PVCs in the antecubital area and minimizing line duration may reduce the risk of HO PVC–associated SAB. Future prospective and larger studies are warranted to identify and refine other potential risk factors.

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