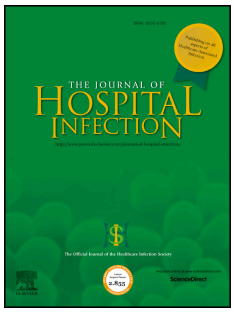
Accepted Manuscript



Nationwide Study on Peripheral Venous Catheter Associated–Bloodstream Infections in Internal Medicine Departments

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PII: S0195-6701(17)30390-0

DOI: 10.1016/j.jhin.2017.07.008

Reference: YJHIN 5163

To appear in: *Journal of Hospital Infection*

Received Date: 23 March 2017

Revised Date: 0195-6701 0195-6701

Accepted Date: 4 July 2017

Please cite this article as: Guembe M, Pérez-Granda MJ, Capdevila JA, Barberán J, Pinilla B, Martín-Rabadán P, Bouza E, on behalf of the NUVE Study Group, Millán J, Pérez de Oteyza C, Muiño A, Villalba M, Cuenca C, Castaño JG, Delgado CM, Zamorano S, Gómez B, Collado JM, Salinas MT, Amat AS, Lázaro JR, Sordo VdV, Sánchez MdV, Benach ÁF, Vidal E, Albiach L, Aparicio JMA, Arroniz ESdA, Casademont i Pou J, Solchaga VP, Castellón FE, Obanos TR, Egurbide Arberas MV, Arana JN, López EG, Gaviria AZ, Clemente IN, Ruíz PC, Salomó AC, Iftimie SM, Castillo AM, Barberá Farré JR, Lavería AO, Ribera MC, Pallarés NB, Suárez PC, Piorno FJC, Andrés NA, Tarazona RER, Zapata MMR, Cerdá

MAC, Nationwide Study on Peripheral Venous Catheter Associated–Bloodstream Infections in Internal Medicine Departments, *Journal of Hospital Infection* (2017), doi: 10.1016/j.jhin.2017.07.008.

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Running title: "Peripheral Catheter–Bloodstream Infections"

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SUMMARY

Background. The use of peripheral venous catheters (PVCs) has increased outside the intensive care unit, as have rates of peripheral venous catheter associated-bloodstream infection (PVC-BSI). The internal medicine department (IMD) is one of the main wards where PVCs are widely used. However, data on the incidence of PVC-BSI and its characteristics in the IMD are scarce.

Aim. Our objective was to assess the incidence of PVC-BSI episodes detected in IMDs in Spain.

Methods. We performed a 1-year multicenter prospective observational cohort study in 14 Spanish IMDs. We included adult patients admitted with at least one PVC and bacteremia. Demographic and clinical data were provided by local coordinators.

Findings. We recorded 70 episodes of PVC-BSI, representing an overall rate of 1.64 PVC-BSI episodes/1,000 IMD admissions. Patients had a mean (SD) age of 67.44 (16.72) years. It was estimated that 25.7% of PVCs were no longer necessary. *Staphylococcus aureus* was the most frequently isolated microorganism (41.7%). Phlebitis was clinically evident in 44 (62.9%) episodes and proved to be an independent predictor of catheter insertion in emergency departments (OR=5.44). The crude and attributable mortality rates were 12.9% and 5.7%, respectively.

Conclusion. Our study shows that PVCs carry a significant risk for bacteremia in Spanish IMDs. Phlebitis is not always clinically evident in patients with bacteremia in this population. Our findings support the need for educational and interventional preventive measures both in IMDs and in emergency departments to reduce the rate of PVC-BSI and associated comorbidities and costs.

Keywords: peripheral venous catheter; bacteremia; *Staphylococcus aureus*; prevalence; phlebitis; peripheral venous catheter-associated bloodstream infection; internal medicine departments.

INTRODUCTION

Central venous catheter (CVC)–related bloodstream infections are one of the most common types of nosocomial infection and are associated with high rates of morbidity and mortality (1, 2). Data on these infections come mainly from intensive care unit patients, where CVCs account for only 4.6% to 18.1% of all catheters used (3-5).

Peripheral venous catheters (PVCs) have become increasingly used in recent years. In addition, exposure to PVCs has become more prolonged, thus leading to an increase in the number of episodes of PVC-associated bloodstream infections (PVC-BSI) (3, 6-13). Rates of PVC-RBSI in Spain have been described between 0.11 and 0.18 PVC-BSI episodes/1,000 admissions (8, 9). Internal medicine departments (IMDs) care for severely ill elderly patients in whom PVCs are widely used (3). However, data on the presence of PVC-BSI and its characteristics in this particular population are scarce.

Our objective was to assess the incidence of PVC-BSI detected in IMDs in Spain.

METHODS

Setting

We performed a multicenter prospective observational cohort study in 14 Spanish IMDs from June 2015 to June 2016. Table 1 shows details of the participating centers.

Inclusion criteria

Adult patients (>18 years) admitted to the IMD with at least 1 PVC and significant bloodstream infection due to the PVC (PVC-BSI).

Data collection and analysis

The demographic and clinical data obtained from the local coordinator for each patient and catheter were as follows: age, sex, Charlson comorbidity index, severity of

sepsis, phlebitis, septic complications (septic metastasis, renal failure), days of antibiotic therapy, extra days of hospitalization, mortality, catheter tip culture, catheter indwelling time, catheter insertion site, location of catheter insertion, need for a catheter, and use of needleless connectors. Surveillance was monitored from the diagnosis of significant bloodstream infection until catheter withdrawal.

All centers followed the standard recommendations collected in pocket leaflets regarding the prevention of infection during catheter insertion and maintenance (supplemental data file).

All withdrawn catheter tips were included in the analysis, regardless of whether they were sent for culture or not (despite this being a requirement in the study).

Definitions

Peripheral venous catheter (PVC). Catheter shorter than 7.62 cm (3 inches).

Significant bloodstream infection. Episode of bacteraemia or fungaemia, in which those pathogens were present in ≥1 blood cultures. We considered commensal microorganisms [coagulase negative Staphylococci (CNS), *Corynebacterium* sp. (except *C. jeikeium*), *Lactobacillus* sp., *Bacillus* sp. and *Propionibacterium* sp., or *viridans* group *Streptococcus* isolates and *C. perfringens*] as probable pathogens when they were recovered in ≥2 blood cultures. Practices to perform blood cultures were all based on international guidelines recommendations and samples obtained through the catheter were excluded (14).

Sepsis. The systemic response to infection, manifesting as 2 or more of the following conditions as a result of infection: temperature >38ºC or <36ºC; heart rate >90

beats per minute; respiratory rate >20 breaths per minute or $PaCO_2$ <32 mm Hg; and white blood cell count >12,000 mm^3, <4,000 mm^3, or >10% immature (band) forms (15).

Severe sepsis. Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status (15).

Septic shock. Sepsis with hypotension despite adequate fluid resuscitation along with perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients receiving inotropic or vasopressor agents may not be hypotensive at the time perfusion abnormalities are measured (15).

Phlebitis. Presence of 1 or more of the following criteria: swelling and erythema >4 mm, tenderness, palpable venous cord, and pain or fever with local symptoms. Isolated swelling is not defined as phlebitis.

PVC-BSI. Presence of positive peripheral blood cultures from a patient with a PVC and clinical manifestations of infection (fever, chills, and/or hypotension) and no apparent source of infection other than the PVC.

Microbiological confirmation of PVC-BSI. Isolation of the same microorganism both in the colonized PVC tip and in blood cultures obtained through a peripheral vein (14).

Peripheral venous catheter colonization. Positivity of the PVC tip culture by the roll-plate technique (≥15 cfu/plate) (14).

An episode of 'significant' bloodstream infection was defined as an episode of bacteremia or fungemia, in which those pathogens were present in ≥ 1 blood cultures.

We considered commensal microorganisms (coagulase negative Staphylococci [CNS], *Corynebacterium* sp. [except *C. jeikeium*], *Lactobacillus* sp., *Bacillus* sp., and *Propionibacterium* sp., or *viridans* group *Streptococcus* isolates and *C. perfringens*) as probable pathogens when they were recovered in ≥ 2 blood cultures.

Statistical analysis

Normally distributed continuous variables were compared using the *t* test; non-normally distributed variables were compared using the Mann-Whitney test, median test, or Kruskal-Wallis test. Categorical variables were evaluated using the chi-squared or 2-tailed Fisher exact test.

Values for continuous variables are expressed as the mean (SD) or median (interquartile range, IQR) and as percentages, with a 95% confidence interval (95% CI), when applicable, for categorical variables. A 2-tailed test was used to determine statistical significance, which was set at $p<0.05$.

We compared PVC-BSI episodes caused by *Staphylococcus aureus* with those caused by other microorganisms and between PVC-BSI episodes with and without phlebitis. The multivariate analysis included variables that showed statistically significant differences between the groups compared in the univariate analysis. For the multivariate analysis, we used binary logistic regression and incorporated variables found to be significant ($p<0.1$) in the univariate analysis. The statistical analysis was performed using PASW Statistics for Windows (SPSS Inc, 18.0, Chicago, Illinois, USA).

Ethics

This study was approved by the local ethics committee of Hospital Gregorio Marañón. Written informed consent was obtained from all patients included in the study.

RESULTS

The 14 IMDs were mainly in teaching institutions (71.4%), and 21.4% were in institutions with ≥500 beds. During the study period, the 14 institutions admitted 302,779 patients, 42,577 of whom were sent to the IMD (**Table 1**). We collected a total of 70 episodes of PVC-BSI from 70 patients, corresponding to 1.64 PVC-BSI episodes/1,000 IMD admissions. This represented approximately 0.28 episodes/1,000 catheter days of exposure based on previous studies of our group in which we reported that >85% of the hospitalized patients had at least 1 venous line for a median of 7 days (4, 5).

Patients and catheters

Patients had a mean (SD) age of 67.44 (16.72) years and 60.0% were men. The mean (SD) comorbidity index (Charlson) was 5.5 (3.25). The median (IQR) catheter indwelling time was 6 (4-12) days, and only 19 catheters (27.1%) had been inserted for ≤96 hours. Most PVCs were inserted in the arm (34.3%), followed by the elbow flexure (25.7%) and the back of the hand (8.6%). The insertion site of the remaining 22 PVCs (31.4%) was not specified. As for department of insertion, 26 PVCs (37.1%) were inserted in the emergency department, and only 21 (30.3%) were inserted in hospital or surgical wards. The department of the remaining 23 (32.3%) PVCs was unknown. The catheter insertion site had been checked 24 hours before the PVC-BSI episode in 75.7% of patients, and 55.7% of the PVCs were closed with needleless connectors. Only 20 (28.6%) of the PVC tips were withdrawn before or at the time of the diagnosis of the PVC-RSI episode. It was estimated that 25.7% of the PVCs in place were no longer necessary on the day of the study (**Table 2**). Phlebitis was observed in 62.9% of cases, and purulence was present in 5 catheters (7.1%).

Of the 70 episodes of PVC-BSI, 52 (74.3%) involved sepsis, whereas 25.7% involved severe sepsis or septic shock. Septic metastasis and/or renal failure was recorded in 14.3% of cases. Patients were under antibiotic therapy for a median (IQR) of 13.00 (7.00-16.25) days. The crude mortality and the attributable mortality rates were 12.9% and 5.7%, respectively (**Table 2**).

Etiology of PVC-BSI episodes

The distribution of the microorganisms isolated in the 70 PVC-BSI episodes was as follows: Gram-positive, 87.5%; Gram-negative, 11.1%; and yeasts, 1.4%. *Staphylococcus aureus* was the most frequently isolated microorganism (41.7%), followed by *Staphylococcus epidermidis* and other coagulase-negative staphylococci (CoNS) (28.5%) (**Table 3**). Among the 38 episodes of *S. aureus* bacteremia, 8 (21.1%) were caused by methicillin-resistant *S. aureus* (MRSA). There were only 2 (2.9%) polymicrobial PVC-BSI episodes.

Only 37 (52.9%) out of the 70 CVC tips were sent for culture. Of them, 26 (70.3%) corresponded to microbiologically confirmed PVC-BSI episodes. The distribution of the 28 microorganisms isolated in the positive PVC tips was as follows: *S. aureus*, 42.9% (26.7% MRSA); *S. epidermidis* and CoNS, 25.0%; *Enterococcus faecalis*, 10.7%; *Klebsiella pneumoniae*, 10.7%; *Pseudomonas aeruginosa*, 7.1%; and *Candida albicans*, 3.6%.

Risk factors for *S. aureus* PVC-BSI and phlebitis in the study population

When we compared the distribution of the study variables for the 70 PVC-SBI episodes between infection caused by *S. aureus* and infection caused by other agents, we did not find any statistically significant differences except for duration of antimicrobial therapy, which was longer for *S. aureus* ($p<0.001$) (**Table 4**).

When we compared the distribution of the study variables according to the presence or absence of phlebitis, we found that the independent risk factors for phlebitis were shorter catheter indwelling time, longer time on antimicrobial therapy, catheter withdrawal before or at the time of the PVC-BSI episode, and catheter insertion in the emergency department ($p<0.001$, $p=0.026$, $p=0.01$, and $p=0.004$, respectively). In the multivariate analysis (which included only catheter days, age, catheter insertion in the emergency department, and idle catheters), we found that insertion of the PVC in the emergency department had an odds ratio (OR) of 5.44 (95% CI, 1.54-19.30; $p=0.009$) for phlebitis. We also detected that, despite the absence of statistical significance, 50% of the catheters that were no longer necessary were associated with phlebitis ($p=0.19$) (**Table 4**).

DISCUSSION

Our data showed that PVC-BSI is a major problem in Spanish IMDs, with an incidence rate of 1.64 episodes/1,000 IMD admissions and *S. aureus* as the causative agent in 41.7% of episodes. Phlebitis was not present in 37.1% of the episodes. We also found that many catheters were no longer necessary during the study period.

PVCs have been increasingly used during the last few years, mainly outside ICUs (11), thus leading to an increase in the number of PVC-BSI episodes. In Spain, rates of 0.11 and 0.18 PVC-BSI episodes/1,000 admissions were found in 2 teaching institutions (8, 9). Lower rates were reported in a multicenter study in which the PVC-BSI rate was 0.05 episodes/1,000 patient-days (16). In IMDs in particular, data on the estimated frequency of PVC-BSI are lacking. In the present study, we found the PVC-BSI rate to be

1.64 episodes/1,000 IMD admissions and an estimation of 0.28 PVC-BSI episodes/1,000 catheter-days, ie, significantly higher than that previously reported for whole institutions.

The mean age of the patients in our study was >65 years, and this has been associated with higher rates of morbidity and mortality, particularly in patients with *S. aureus* bacteremia (17). Our attributable mortality rate was 5.7%, although follow-up was not long. A recent study found that 85% of patients aged ≥65 years died within 5 years (18). We showed that most PVC-BSI episodes were caused by *S. aureus* (41.7%), as reported by other authors (9, 16, 19-21). However, we did not find any risk factors associated with *S. aureus* PVC-BSI. We only found a significant difference between *S. aureus* PVC-BSI and non-*S. aureus* PVC-RBSI regarding the days of antimicrobial therapy (43.01 vs. 26.58 days, $p<0.001$).

The rate of phlebitis (62.9%) was surprisingly low, as might be expected in this bacteremic population, thus supporting the observation that phlebitis is not a good marker for bacteremia. We also demonstrated that phlebitis was not associated with longer catheter indwelling times, in contrast with reports from other authors (22) and in support of previous recommendations not to replace PVCs every 96 hours (23-26). It has been hypothesized that phlebitis is more frequent in PVCs as a result of chemical irritation of the vein wall by the substances administered and that risk is higher when the course and calibre of the vein are lower, as this facilitates contact perfusion with the vascular endothelium (10, 27). The most important finding was that 22 of the 26 catheters (84.6%) from bacteremic patients that had been inserted in the emergency department were associated with phlebitis, with an OR of 5.44 of phlebitis among catheters that were inserted in the emergency department ($p=0.009$), as also shown in

242 whole hospital populations (12, 28). These findings strongly support adherence to the
243 recommendation to insert catheters under aseptic conditions or replace them in <48 h if
244 aseptic conditions are not followed during insertion. The same recommendations for
245 central venous catheters should also be applied in PVCs (29).

246 Another important issue in the management of PVCs was the rate of idle
247 catheters. Several studies showed rates of 16% to 38% in both CVCs and PVCs (3, 11, 30).
248 We found that 25.1% of the PVCs were no longer necessary, thus implying that future
249 preventive measures to reduce the number of unnecessary PCVs should include daily
250 monitoring of catheter use based on a check-list, as performed with CVCs (26, 29).

251 Of note, 47.1% of the withdrawn PVC tips were not sent for culture, despite this
252 being a study requirement. This shortcoming should be considered in future
253 recommendations for the management of PVC-BSI, and physicians should be encouraged
254 to send the tip for culture to confirm the PVC-BSI episode (26). Moreover, 11 (29.7%) of
255 the 37 cultured PVC tips were negative, thus PVC-BSI episodes could not be
256 microbiologically confirmed.

257 Finally, the 70 PVC-BSI episodes were a major problem in the IMD not only
258 because of their related comorbidities, but also because they represented an extra cost
259 of €1,060,570 in the 14 institutions. The question of cost was recently assessed in a
260 Spanish study in which the authors estimated that the extra cost of an episode of
261 bacteremia was €15,151 (31).

262 The main limitation of this study is that our data can only be extrapolated to
263 bacteremic older patients admitted mainly to IMDs from hospitals with <500 beds.

Our findings demonstrate that PVC-BSI is still a major problem in IMDs and that introducing mandatory educational and interventional preventive measures is essential, if we are to reduce the frequency of PVC-BSI and associated comorbidities and overall costs (29, 32).

ACKNOWLEDGEMENTS

We thank Thomas O'Boyle for his help in the preparation of the manuscript.

We thank the members of the NUVE study group for their contribution to the study:

Hospital General Universitario Gregorio Marañón (Madrid): Jesús Millán, Carlos Pérez de Oteyza, Antonio Muiño, Mariví Villalba, Carmen Cuenca, Jesús García Castaño, Cecilia Muñoz Delgado, Sonia Zamorano, Beatriz Gómez, José Manuel Collado.

Hospital L'Esperit Sant (Cataluña): Miguel Torres Salinas, Alex Smithson Amat, Javier Ramos Lázaro.

Hospital de Santa Bárbara (Castilla La Mancha): Valentín del Villar Sordo, Mario del Valle Sánchez.

Hospital de Mataró (Cataluña): Ángela Felip Benach, Elena Vidal, Laia Albiach.

Hospital de Txagorritxu (País Vasco): José Manuel Agud Aparicio, Esther Saéz de Adana Arroniz.

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Hospital Santos Reyes (Burgos): Pedro Cancelo Suárez, Francisco Javier Cepeda Piorno, Noelia Arenal Andrés, Raquel Elisa Rodríguez Tarazona.

Hospital Universitario de Guadalajara (Castilla La Mancha): Manuel Miguel Rodríguez Zapata, María Asunción Costa Cerdá.

Potential conflicts of interest. The authors declare no conflicts of interest.

Financial support: M. Guembe is supported by the Miguel Servet Program (ISCIII-MICINN, CP13/00268) from the Health Research Fund (FIS) of the Carlos III Health Institute (ISCIII), Madrid Spain. The study was partially funded by the European Regional Development Fund (FEDER) “A way of making Europe” and Fundación Española de Medicina Interna (FEMI).

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ON-LINE SUPPLEMENTARY FIGURE 1: Pocket leaflet describing the prevention of infection during catheter insertion and maintenance

Table 1. Description of the participating institutions

N=14	
Teaching institution, N (%)	10 (71.4)
Public institution, N (%)	13 (82.9)
<500 beds, N (%)	11 (78.6)
Mean (SD) population	223,376.6 (110,022.7)
Mean (SD) no. of hospital admissions/2014 (>24 h)	21,627.1 (14,772.0)
Mean (SD) no. of IMD admissions/2014 (>24 h)	3,041.2 (1,453.3)
Mean (SD) total no. of hospital beds	409.1 (296.2)
Mean (SD) total no. of beds in the IMD	67.6 (25.4)
Mean (SD) days of hospital stay	7.9 (1.1)

SD, standard deviation; **IMD**, internal medicine department.

Table 2. Patient and catheter data for the PVC-BSI episodes

Characteristic	N (%)
Patients (N=70)	
Mean (SD) age, years	67.44 (16.72)
Male sex	42 (60.0)
Mean (SD) comorbidity index (Charlson)	5.5 (3.25)
Type of infection	
Sepsis	52 (74.3)
Severe sepsis	17 (24.3)
Septic shock	1 (1.4)
Complications	
None	60 (85.7)
Septic metastasis	6 (8.6)
Renal failure	2 (2.9)
> 1 complication	2 (2.9)
Median (IQR) days of antibiotic therapy	13 (7.00-16.25)
Crude mortality	9 (12.9)
Attributable mortality	4 (5.7)
Catheters (N=70)	
Microbiological culture	
Positive	26/37 (70.3)
Negative	11/37 (29.7)

Non-cultured	33/70 (47.1)
Median (IQR) catheter days	6 (4-12)
Catheter indwelling time	
≤96 hours	19 (27.1)
>96 hours	51 (72.9)
Insertion site	
Right elbow flexure	11 (15.7)
Left elbow flexure	7 (10.0)
Right arm	14 (20.0)
Left arm	10 (14.3)
Back of the right hand	4 (5.7)
Back of the left hand	2 (2.9)
Other	22 (31.4)
Department where catheter was inserted	
Emergency	26 (37.1)
Hospital ward	17 (24.3)
Surgery	4 (5.7)
Other	23 (32.3)
Catheter insertion site revised at least 24 hours before PVC-BSI episode	53 (75.7)

Phlebitis	44 (62.9)
Purulence	5 (7.1)
Use of needleless connectors	39 (55.7)
Use of disinfectable needleless connectors	35/39 (89.7)
Time of catheter withdrawal	
Before or at the same time of PVC-BSI episode	20 (28.6)
After PVC-BSI episode	50 (71.4)
No. of idle catheters	18 (25.7)

SD, standard deviation; **IQR**, interquartile range; **ICU**, intensive care unit; **PVC-BSI**, peripheral venous catheter associated–bloodstream infection.

Table 3. Microorganisms isolated in the PVC-BSI episodes

Microorganism	N (%)
Gram +	**63 (87.5)**
Methicillin-susceptible *Staphylococcus aureus*	30 (41.7)
Methicillin-resistant *Staphylococcus aureus*	8 (11.1)
Staphylococcus epidermidis	14 (19.4)
CNS	6 (8.3)
Enterococcus faecalis	4 (5.6)
Propionibacterium acnes	1 (1.4)
Gram –	**8 (11.1)**
Klebsiella pneumoniae	4 (5.6)
Pseudomonas aeruginosa	3 (4.2)
Escherichia coli	1 (1.4)
Yeasts	**1 (1.4)**
Candida albicans	1 (1.4)

CNS, coagulase-negative staphylococci.

Table 4. Risk factors for *S. aureus* PVC-BSI and phlebitis

Variable	SAB N=38	No SAB N=32	p	Phlebitis N=44	No phlebitis N=26	p
Median (IQR) days of antimicrobial therapy	14.50 (11.75-21.50)	8.00 (7.00-14.00)	<0.001	14.00 (10.00-19.50)	9.50 (7.00-15.25)	0.02
Median (IQR) catheter days	6.00 (4.00-9.00)	7.00 (4.25-14.75)	0.27	5.00 (4.00-7.00)	12.00 (6.00-24.00)	<0.001
Catheter indwelling time, N (%)			0.71			0.005
≤96 hours (N=19)	11 (28.9%)	8 (25.0%)		17 (38.6%)	2 (7.7%)	
>96 hours (N=51)	27 (71.1%)	24 (75.0%)		27 (61.4%)	24 (92.3%)	
Time of catheter withdrawal, N (%)			0.94			0.01
Before or at the same time of PVC-BSI episode (N=20)	11 (28.9%)	9 (28.1%)		36 (81.8%)	14 (53.8%)	
After PVC-BSI episode (N=50)	27 (71.1%)	23 (71.9%)		8 (18.2%)	12 (46.2%)	
Septic complications, N (%)			0.70			0.61
One or more (N=10)	6 (15.8%)	4 (12.5%)		7 (15.9%)	3 (11.5%)	
None (N=60)	32 (84.2%)	28 (87.5%)		37 (84.1%)	23 (88.5%)	
Attributable mortality, N (%)	2 (5.3%)	2 (6.3%)	0.63	1 (2.3%)	3 (11.6%)	0.14

Severe sepsis or septic shock (N=18), N (%)	13 (34.2%)	5 (15.6%)	0.08	12 (27.3%)	6 (23.1%)	0.70
Phlebitis (N=44), N (%)	27 (71.1%)	17 (53.1%)	0.12	NA	NA	NA
Catheter insertion in emergency department (N=26), N (%)	17 (44.4%)	9 (28.1%)	0.15	22 (50.0%)	4 (15.4%)	0.004
Idle catheters (N=18), N (%)	11 (28.9%)	7 (21.9%)	0.50	9 (20.5%)	9 (34.6%)	0.19

IQR, interquartile range; **SAB**, *Staphylococcus aureus* bacteremia; **PVC-BSI**, peripheral venous catheter associated-bloodstream infection; **NA**, not applicable.