Short-Term Peripheral Venous Catheter-Related Bloodstream Infections: Evidence for Increasing Prevalence of Gram-Negative Microorganisms from a 25-Year Prospective Observational Study

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ABSTRACT The aim of this study was to describe the etiology and outcome of short-term peripheral venous catheter (PVC)-related bloodstream infections (PVCRBSI) in a 25-year period (1992 to 2016) and to identify predictive factors of Gram-negative PVCRBSI. This was a prospective observational study including all episodes of PVCRBSI. A multivariate logistic regression model adjusted for calendar year was built to explore factors associated with a Gram-negative bacterial etiology. Over the study period, 711 episodes of PVCRBSI were identified. Incidence rate of PVCRBSI increased from 0.06 to 0.13 episodes/1,000 patient-days. A Gram-negative bacterial etiology was demonstrated in 162 (22.8%) episodes. There was a significant increase in the proportion of Gram-negative infections (22.6% in 1992 to 1996 versus 33.2% in 2012 to 2016). Independent predictive factors of Gram-negative PVCRBSI were the following: being in the hospital for more than 7 days with a catheter *in situ* for more than 3 days (adjusted odds ratio [aOR], 1.80; 95% confidence interval [CI], 1.20 to 2.69), surgery in the previous month (aOR, 2.39; 95% CI, 1.40 to 4.09), and antimicrobial treatment with beta-lactams (aOR, 1.80; 95% CI, 1.16 to 2.78). In conclusion, we reported an increase in the prevalence of Gram-negative PVCRBSI over the last 25 years. Factors associated with a Gram-negative bacterial etiology were being in the hospital for more than 7 days with a catheter *in situ* for more than 3 days, having undergone surgery, and having received antimicrobial treatment with beta-lactams.

KEYWORDS Gram negative, bacteremia, bloodstream infections, peripheral venous catheter, phlebitis

Short-term peripheral venous catheters (PVCs) are among the most frequently used medical devices, and recent studies estimated the prevalence of hospitalized patients with an indwelling PVC between 23% and 78% (1–5). Two recent literature reviews (6, 7) describe an incidence rate of PVC-related bloodstream infections (PVCRBSI) of 0.5 (95% confidence interval [CI], 0.2 to 0.7) per 1,000 days of PVC use or between 0.02 and 0.2 per 1,000 patient days. Currently, evidence-based internationally endorsed guidelines regarding the management of PVCRBSI are not available, and in the vast majority of cases, the management of these infectious complications is based on the recommendations for central venous catheter (CVC)-related bloodstream infec-

tions (CVCRBSI) (8). These guidelines suggest universal empirical antibiotic coverage active against staphylococci, while empirical treatment for Gram-negative bacilli is suggested only in patients with sepsis, neutropenia, a femoral catheter, or a known distal focus of Gram-negative bacillus infection. However, a growing number of reports are highlighting the increase in Gram-negative bacteria as the etiology of CVCRBSI (9–12), a finding which has yet to be fully explored for PVCRBSI.

Given the high number of patients at risk and the associated morbidity and mortality, estimated to be as high as 18% (13), a comprehensive assessment of the characteristics of PVCRBSI seems to be of utmost importance in order to guide the management of this complication.

The aim of our study was to describe the incidence, etiology, clinical characteristics, and outcomes of patients with PVCRBSI admitted over a 25-year period (1992 to 2016) in a large tertiary university hospital and to identify predictive factors of Gram-negative PVCRBSI.

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RESULTS

Patient characteristics, incidence rate, and outcomes. During the study period (1992 to 2016), 27,386 episodes of bacteremia were registered. Among those, 3,842 (14.0%) were classified as catheter-related bloodstream infections, of which 3,337 (12.2%) were of monomicrobial etiology. Of all monomicrobial catheter-related bloodstream infections, 2,626 (9.6%) were CVCRBSI, and 711 (2.6%) were PVCRBSI. Patient characteristics are detailed in Table 1. The overall incidence rate of PVCRBSI increased from 0.06 episodes/1,000 patient days in 1992 to 0.13 episodes/1,000 patient days in 2016; interestingly, in the same period we also detected an increase in the incidence rate of CVCRBSI from 0.10 episodes/1,000 patient days in 1992 to 0.26 episodes/1,000 patient days in 2016 (Fig. 1). The prevalence of PVCRBSI was higher in the first week after hospital admission (54.9% of the total cases), and 28.3% of patients were diagnosed within the first 3 days after catheter placement.

Overall, 10.5% of patients did not present with phlebitis and were diagnosed as a result of a positive catheter tip culture in the absence of other apparent infectious foci. Phlebitis was less common in patients with PVCRBSI due to Gram-negative bacilli than in patients with a Gram-positive bacterial etiology (80.9% versus 92.4%; P value of <0.001); interestingly, while presentation with phlebitis was not significantly different among patients infected with Gram-negative bacteria, patients with *Staphylococcus aureus* PVCRBSI had a higher proportion of phlebitis than patients infected with other Gram-positive cocci (94.8% versus 88.7%; P value of 0.009). Nevertheless, a significant difference in rates of phlebitis occurrence between infections with Gram-negative bacteria and those with Gram-positive bacteria was still evident even after excluding *Staphylococcus aureus* from the pool of Gram-positive bacteria (80.9% versus 88.7%; P value of 0.033).

PVC tip culture was more frequently performed in patients with a Gram-negative PVCRBSI (32.1% versus 20.6%; P value of <0.001) than in those with Gram-positive PVCRBSI. Specifically, PVC tip culture was less frequently performed in patients with *Staphylococcus aureus* bacteremia (19.0% versus 26.9%; P value of 0.001), possibly because in these cases the diagnosis was more evident for the physician in charge. Characteristics of patients with a positive PVC tip culture and patients without one are presented in Table 2. Phlebitis, a requirement for PVCRBSI diagnosis, was present in all patients without a PVC tip culture and in only 51.3% of patients with a positive PVC tip culture. Patients with a positive PVC tip culture were more likely to have a longer hospital stay and have a PVC *in situ* for a longer period of time. Cirrhosis, diabetes, and solid-organ malignancies were less frequent in patients with a positive PVC tip culture, while cardiac disease was more common than in patients without a PVC tip culture. The proportion of patients with Gram-negative PVCRBSI was higher in subjects with a positive PVC tip culture (31.2% versus 20.2%; P value of 0.004).

TABLE 1 Characteristics of patients with PVCRBSI

Parameter	Value for the parameter ($n = 711$)[a]
Median age (range [yr])	67 (55–77)
Male sex	467 (65.7)
Phlebitis	636 (89.5)
Catheter culture	
Negative	12 (1.7)
Positive	154 (21.7)
Not performed	545 (76.7)
Prior hospital admission	99 (13.9)
Days since hospital admission	
Median no. of days (range)	7 (4–12)
0–7	390 (54.9)
8–14	161 (22.6)
15–21	60 (8.4)
>21	68 (9.6)
Unknown	32 (4.5)
Days since catheter placement	
Median no. of days (range)	5 (3–7)
0–3	201 (28.3)
4–6	245 (34.5)
7–9	122 (17.2)
10–12	46 (6.5)
13–15	15 (2.1)
16–18	6 (0.8)
>19	7 (1.0)
Unknown	69 (9.7)
Fever	690 (97.0)
Shock	19 (2.7)
Prior surgery	77 (10.8)
Prior nonsurgical invasive procedure	81 (11.4)
Urinary catheter	133 (18.7)
Cirrhosis	102 (14.3)
Diabetes	163 (22.9)
Pulmonary disease	57 (8.0)
HIV infection	23 (3.2)
Chronic kidney disease	67 (9.4)
Cardiac disease	249 (35.0)
Hematological malignancy	53 (7.5)
Solid organ malignancy	112 (15.8)
Neutropenia	14 (2.0)
Solid organ transplant	32 (4.5)
Corticosteroid therapy	129 (18.1)
McCabe, ultimately or rapidly fatal outcome	278 (39.1)
7-Day mortality	26 (3.7)
30-Day mortality	53 (7.5)
Persistent bacteremia	33 (4.6)
Correct empirical treatment	386 (54.3)
Prior antibiotic treatment	169 (23.8)
Microbial etiology	
Gram-positive cocci	533 (75.0)
Staphylococcus aureus	327 (46.0)
Coagulase-negative staphylococci	178 (25.0)
Enterococcus spp.	26 (3.7)
Gram-negative bacilli	162 (22.8)
Klebsiella spp.	40 (5.6)
Pseudomonas aeruginosa	32 (4.5)
Escherichia coli	29 (4.1)
Enterobacter spp.	28 (3.9)
Serratia spp.	5 (0.7)
Acinetobacter spp.	5 (0.7)
Candida spp.	9 (1.3)

[a]Values are given as number of patients (percentage) unless otherwise indicated.
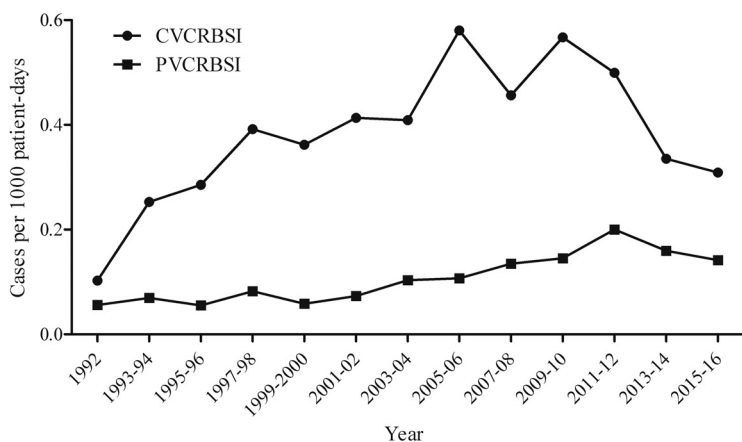
FIG 1 Incidence rate of catheter-related bloodstream infections.

Correct empirical treatment was administered in 54.3% of patients, and 4.6% of the patients had persistent bacteremia under active antibiotic treatment. Incorrect empirical antibiotic treatment was more frequently administered in patients with PVCRBSI due to *Pseudomonas aeruginosa* (37.5% versus 55.1%, *P* value = 0.051) and *Enterobacteriaceae* resistant to third-generation cephalosporins (27.8% versus 55.0%; *P* value of 0.022) and methicillin-resistant coagulase-negative staphylococci (24.2% versus 58.9%; *P* value of <0.001).

Overall in-hospital mortality rates at 7 and 30 days after the diagnosis of PVCBRSI were 3.7% and 7.5%, respectively. No difference in 7- and 30-day overall in-hospital mortality rates was observed between patients with Gram-negative versus Gram-positive PVCRBSI, while persistent bacteremia was more frequent among patients with Gram-positive infections (Table 3). Interestingly, overall in-hospital mortality was not significantly different from that in patients with CVCRBSI (4.6% and 8.7% at 7 and 30 days; *P* values of 0.273 and 0.296, respectively).

Microbiological etiology. During the study period, 533 cases (75.0%) were caused by Gram-positive cocci, 162 (22.8%) were caused by Gram-negative bacilli, and 9 (1.3%) were caused by *Candida* spp. Microbiological etiology of PVCRBSI is described in Table 1. Notably, over the study period (Fig. 2 and 3) there was a significant increase in the proportion of PVCRBSI due to Gram-negative bacilli (*P* value of <0.001), with a corresponding reduction of Gram-positive coccus etiology (*P* value of <0.001), while the proportion of PVCRBSI due to *Candida* spp. remained stable over time (*P* value of 0.865). The majority of Gram-negative PVCRBSI were due to *Klebsiella* spp. (24.7%), followed by *Pseudomonas aeruginosa* (19.8%) and *Escherichia coli* (17.9%). The proportion of isolates resistant to third-generation cephalosporins was 17.5% among *Klebsiella* spp., 17.2% for *Escherichia coli*, and 21.4% among *Enterobacter* spp., while 9.4% and 15.6% of *Pseudomonas aeruginosa* isolates were resistant to ceftazidime and carbapenems, respectively. Among Gram-positive cocci, 61.4% of episodes were due to *Staphylococcus aureus* (9.5% resistant to methicillin), 33.4% were due to coagulase-negative staphylococci (53.4% resistant to methicillin), and 4.9% were due to *Enterococcus* spp. (26.9% resistant to ampicillin).

Predictive factors for developing Gram-negative PVCRBSI. Demographic, epidemiological, and clinical characteristics of patients with PVCRBSI due to Gram-negative and Gram-positive bacteria are compared in Table 3. Notably, a Gram-negative bacterial etiology was more frequent among patients who were admitted to the hospital for more than 7 days and who had undergone surgical intervention in the previous 30 days. Moreover, PVCBRSI due to Gram-negative bacteria was more common in patients who had received antimicrobial treatment in the previous month, especially with beta-lactams and linezolid, and in those receiving antibiotics at the time of PVCRBSI diagnosis. On the other hand, a Gram-positive bacterial etiology was more frequent in

TABLE 2 Comparison of patients with PVCRBSI with a positive PVC tip culture and patients with PVCRBSI without an available PVC tip culture

Parameter	Value for the group[a]		P value[b]
	Positive PVC tip culture (n = 154)	PVC tip culture not performed (n = 545)	
Median age (range [yr])	67 (50–77)	67 (55–78)	0.346
Male sex	96 (62.3)	362 (66.4)	0.290
Phlebitis	79 (51.3)	545 (100.0)	**<0.001**
Prior hospital admission	21 (13.6)	77 (14.1)	0.877
Days since hospital admission			
Median no. of days (range)	8 (5–13)	6 (4–11)	**0.002**
0–7	64 (41.6)	317 (58.2)	**<0.001**
>7 or unknown	90 (58.4)	228 (41.8)	
Days since catheter placement			
Median no. of days (range)	5 (4–8)	5 (3–7)	**0.014**
0–3	28 (18.2)	169 (31.0)	**0.002**
>3 or unknown	126 (81.8)	376 (69.0)	
Fever	149 (96.8)	529 (97.1)	0.842
Shock	4 (2.6)	13 (2.4)	0.880
Prior surgery	22 (14.3)	53 (9.7)	0.106
Prior nonsurgical invasive procedure	14 (9.1)	65 (11.9)	0.326
Urinary catheter	29 (18.8)	100 (18.3)	0.892
Cirrhosis	7 (4.5)	92 (16.9)	**<0.001**
Diabetes	25 (16.2)	134 (24.6)	**0.029**
Pulmonary disease	13 (8.4)	44 (8.1)	0.883
HIV infection	8 (5.2)	15 (2.8)	0.134
Chronic kidney disease	8 (5.2)	56 (10.3)	0.054
Cardiac disease	75 (48.7)	169 (31.0)	**<0.001**
Hematological malignancy	10 (6.5)	43 (7.9)	0.563
Solid organ malignancy	11 (7.1)	101 (18.5)	**0.001**
Neutropenia	4 (2.6)	10 (1.8)	0.551
Solid organ transplant	4 (2.6)	27 (5.0)	0.210
Corticosteroid therapy	28 (18.2)	100 (18.3)	0.962
McCabe, ultimately or rapidly fatal outcome	44 (28.6)	229 (42.0)	**0.003**
Previous ABT[c]	38 (24.7)	128 (23.5)	0.759
Beta-lactams	26 (16.9)	80 (14.7)	0.501
Penicillins	13 (8.4)	39 (7.2)	0.591
Third-generation cephalosporins	11 (7.1)	32 (5.9)	0.562
Carbapenems	1 (0.6)	17 (3.1)	0.088
Aminoglycosides	4 (2.6)	2 (0.4)	**0.023**
Glycopeptides	3 (1.9)	10 (1.8)	0.927
Fluoroquinolones	9 (5.8)	44 (8.1)	0.356
Linezolid	2 (1.3)	6 (1.1)	0.839
Current ABT	23 (14.9)	113 (20.7)	0.108
Betalactams	15 (9.7)	61 (11.2)	0.609
Penicillins	7 (4.5)	30 (5.5)	0.639
Third-generation cephalosporins	7 (4.5)	21 (3.9)	0.699
Carbapenems	0 (0.0)	5 (0.9)	0.233
Aminoglycosides	2 (1.3)	7 (1.3)	0.989
Glycopeptides	1 (0.6)	5 (0.9)	0.999
Fluoroquinolones	5 (3.2)	40 (7.3)	0.068
Linezolid	0 (0.0)	1 (0.2)	0.999

[a]Values are given as number of patients (percentage) unless otherwise indicated.
[b]Significant values are in boldface.
[c]ABT, antibiotic therapy.

patients with phlebitis, cirrhosis, and chronic kidney failure and in those with a worse McCabe prognostic score.

After multivariate logistic regression analysis adjusted for calendar year (Table 4), independent predictive factors of developing Gram-negative PVCRBSI were the following: being in the hospital for more than 7 days with a catheter *in situ* for more than 3

TABLE 3 Characteristics of patients with PVCRBSI due to Gram-positive and Gram-negative bacteria

Parameter	Value for the group[a]		P value[b]
	Gram-positive infection (n = 540)	Gram-negative infection (n = 162)	
Median age (range [yr])	67 (55–77)	66 (52–78)	0.480
Male sex	348 (64.4)	111 (68.5)	0.339
Phlebitis	499 (92.4)	131 (80.9)	**<0.001**
PVC culture			**0.009**
Negative	8 (1.5)	4 (2.5)	
Positive	103 (19.1)	48 (29.6)	
Not performed	429 (79.4)	110 (67.9)	
Prior hospital admission	74 (13.7)	24 (14.8)	0.720
Days since hospital admission			
Median no. of days (range)	6 (4–10)	8 (5–17)	**<0.001**
0–7	319 (59.1)	69 (42.6)	**<0.001**
>7 or unknown	221 (40.9)	93 (57.4)	
Days since catheter placement			
Median no. of days (range)	5 (3–7)	5 (3–7)	0.129
0–3	162 (30.0)	38 (23.5)	0.106
>3 or unknown	378 (70.0)	124 (76.5)	
Fever	527 (97.6)	154 (95.1)	0.114
Shock	13 (2.4)	6 (3.7)	0.407
Prior surgery	40 (7.4)	36 (22.2)	**<0.001**
Prior non-surgical invasive procedure	58 (10.7)	23 (14.2)	0.227
Urinary catheter	93 (17.2)	38 (23.5)	0.074
Cirrhosis	92 (17.0)	9 (5.6)	**<0.001**
Diabetes	130 (24.1)	31 (19.1)	0.190
Pulmonary disease	44 (8.1)	13 (8.0)	0.960
HIV infection	18 (3.3)	4 (2.5)	0.580
Chronic kidney disease	58 (10.7)	9 (5.6)	**0.049**
Cardiac disease	200 (37.0)	47 (29.0)	0.061
Hematological malignancy	44 (8.1)	9 (5.6)	0.273
Solid organ malignancy	82 (15.2)	28 (17.3)	0.519
Neutropenia	10 (1.9)	3 (1.9)	0.999
Solid organ transplant	27 (5.0)	5 (3.1)	0.306
Corticosteroid therapy	92 (17.0)	33 (20.4)	0.331
McCabe, ultimately or rapidly fatal outcome	227 (42.0)	45 (27.8)	**0.001**
7-Day mortality	21 (3.9)	5 (3.1)	0.635
30-Day mortality	40 (7.4)	12 (7.4)	0.999
Persistent bacteremia	30 (5.6)	2 (1.2)	**0.021**
Correct empirical treatment	305 (56.5)	80 (49.4)	0.111
Previous ABT[c]	107 (19.8)	55 (34.0)	**<0.001**
Beta-lactams	61 (11.3)	43 (26.5)	**<0.001**
Penicillins	22 (4.1)	26 (16.0)	**<0.001**
Third-generation cephalosporins	29 (5.4)	14 (8.6)	0.128
Carbapenems	6 (1.1)	12 (7.4)	**<0.001**
Aminoglycosides	6 (1.1)	1 (0.6)	0.999
Glycopeptides	8 (1.5)	5 (3.1)	0.190
Fluoroquinolones	36 (6.7)	14 (8.6)	0.391
Linezolid	3 (0.6)	5 (3.1)	**0.019**
Current ABT	94 (17.4)	40 (24.7)	**0.039**
Beta-lactams	51 (9.4)	22 (13.6)	0.130
Penicillins	20 (3.7)	15 (9.3)	**0.004**
Third-generation cephalosporins	22 (4.1)	4 (2.5)	0.343
Carbapenems	3 (0.6)	2 (1.2)	0.327
Aminoglycosides	7 (1.3)	1 (0.6)	0.689
Glycopeptides	6 (1.1)	1 (0.6)	0.999
Fluoroquinolones	34 (6.3)	11 (6.8)	0.822
Linezolid	0 (0.0)	1 (0.6)	0.231

[a]Values are given as number of patients (percentage) unless otherwise indicated.
[b]Significant values are in boldface.
[c]ABT, antibiotic therapy.
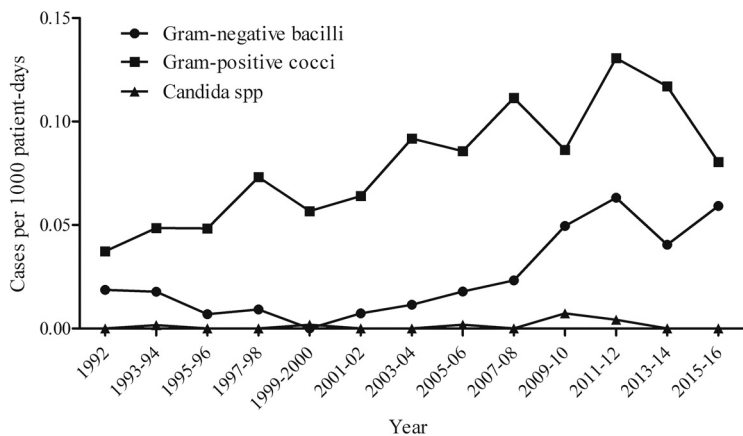
FIG 2 Incidence rate of PVCRBSI according to microbial etiology.

days (adjusted odds ratio [aOR], 1.80; 95% CI, 1.20 to 2.69), having undergone surgery in the previous month (aOR, 2.39; 95% CI, 1.40 to 4.09), and having received antimicrobial treatment with beta-lactams in the previous month or concomitantly with the episode of bacteremia (aOR, 1.80; 95% CI, 1.16 to 2.78). Factors associated with a lower risk of Gram-negative PVCRBSI were presenting with phlebitis (aOR, 0.35; 95% CI, 0.20 to 0.63), having cirrhosis (aOR, 0.40; 95% CI, 0.19 to 0.86), or a cardiovascular comorbidity (aOR, 0.56; 95% CI, 0.36 to 0.85) and a worse McCabe prognostic score (aOR, 0.57; 95% CI, 0.37 to 0.88). The Hosmer-Lemeshow goodness-of-fit test yielded a nonsignificant result (P value of 0.303). No collinearity was detected in the multivariable model (variance inflation factor [VIF] range, 1.020 to 2.163).

Finally, a subgroup analysis was performed in patients with a positive PVC culture. The only two factors associated with a Gram-negative bacterial etiology were the presence of phlebitis (aOR, 0.383; 95% CI, 0.186 to 0.787) and previous surgery (aOR, 2.480; 95% CI, 0.946 to 6.500), even though the latter did not reach statistical significance, probably due to the smaller sample size.

DISCUSSION

In this prospective observational study, we described the characteristics and outcomes of 711 peripheral venous catheter-related bloodstream infections diagnosed over 25 years at our center. To our knowledge, this is the largest prospective study analyzing PVCRBSI. The incidence rate of PVCRBSI doubled over time, reaching 0.13 episodes/1,000 patient days in 2016, half the incidence rate of CVCRBSI. However, a trend toward a progressive reduction has been observed during recent
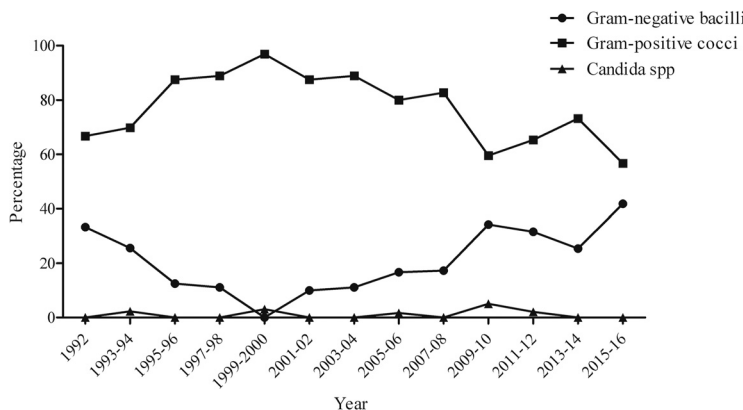
FIG 3 Microbial etiology of PVCRBSI.

TABLE 4 Logistic regression analysis for factors associated with Gram-negative bacillus bacteremia in patients with PVCRBSI

Factor	OR (95% CI)	P value for unadjusted OR[a]	aOR (95% CI)	P value for aOR[a]
Year of diagnosis		<**0.001**		<**0.001**
1992–1996	Reference		Reference	
1997–2001	0.226 (0.087–0.590)	**0.002**	0.277 (0.101–0.763)	**0.013**
2002–2006	0.566 (0.285–1.126)	0.105	0.883 (0.416–1.876)	0.747
2007–2011	1.268 (0.712–2.260)	0.420	1.821 (0.951–3.486)	0.070
2012–2016	1.701 (0.958–3.018)	0.070	2.322 (1.199–4.495)	**0.012**
Hospital stay of >7 days with a catheter *in situ* for >3 days	1.951 (1.367–2.785)	<**0.001**	1.799 (1.204–2.688)	**0.004**
Prior surgery	3.540 (2.172–5.769)	<**0.001**	2.388 (1.396–4.085)	<**0.001**
Prior or current beta-lactam therapy	2.401 (1.626–3.547)	<**0.001**	1.797 (1.161–2.782)	**0.009**
Phlebitis	0.368 (0.224–0.606)	<**0.001**	0.351 (0.197–0.625)	<**0.001**
Cirrhosis	0.288 (0.142–0.586)	**0.001**	0.399 (0.186–0.855)	**0.018**
Cardiac disease	0.702 (0.480–1.028)	0.069	0.556 (0.364–0.851)	**0.007**
McCabe, ultimately or rapidly fatal outcome	0.522 (0.356–0.765)	**0.001**	0.569 (0.368–0.878)	**0.011**

[a]Values in boldface are significant.

years, which could be attributable to the implementation since 2012 of a program similar to Bacteremia Zero for CVC (14, 15) that was implemented in our intensive care unit (ICU) in 2010 and significantly reduced the incidence of CVCRBSI (Fig. 1). Importantly, even though patients with a CVC were more severely ill and had a higher number of comorbidities, overall in-hospital mortality rates at both 7 and 30 days did not differ significantly between groups. This finding prompts a high level of suspicion for the diagnosis of PVCRBSI, which must be managed rapidly and appropriately.

Over the last 25 years, we observed a significant increase in PVCRBSI due to Gram-negative bacteria. This change in the epidemiology has been described in several reports regarding CVCRBSI (9–12, 16, 17), but data concerning PVCRBSI are scarce. A recent study by Sato et al. described a similar prevalence of Gram-negative infections (35.8%) in the 2010-2015 period (18) while a Spanish nationwide study conducted only in internal medicine departments showed a Gram-negative bacillus prevalence of 11.1% (19).

In our study, factors associated with a Gram-negative bacterial etiology were prior surgical intervention, antibiotic treatment in the previous 30 days or during the episode of bacteremia, and having a PVC *in situ* for more than 3 days in patients being admitted to the hospital for more than 7 days.

Prior surgical intervention has already been described as a risk factor for Gram-negative bacteremia (20). We may speculate that in this subset of patients, a higher frequency of Gram-negative bacteremia (even without overt infection) may be a predisposing factor of catheter colonization and subsequent infection. All the patients included in the study were evaluated for surgery-related infectious complications, and patients who had such a complication were excluded even if they had concomitant phlebitis due to the presence of another source of infection.

To our knowledge no studies have evaluated the relationship between length of hospital stay with a catheter *in situ* and the risk of Gram-negative infection. This finding may be related to a change in the Gram-negative proportion of bacteria in the skin microbiota of the hospitalized patients (21), but further studies are needed in order to better elucidate the role of skin flora in the pathophysiology of catheter-related infection (22).

Calendar year was also found to be an independent predictor of Gram-negative bacteremia, suggesting that some epidemiological or environmental factors not included in our analysis may be related to the increase of Gram-negative PVCRBSI seen in recent years; nevertheless, the implementation of prevention bundles which may be more effective in reducing Gram-positive infections (23, 24) may partially explain this finding.

Clinical signs of phlebitis were present in almost 90% of patients with a confirmed

PVCRBSI; however, 1 out of 10 patients did not present with local inflammation, and the diagnosis was made only thanks to a positive catheter tip culture yielding the same pathogen isolated in the peripheral blood cultures. In the clinical setting, this result reflects the importance of having a dedicated team to search for the source of all episodes of bacteremia. Current clinical practice guidelines (8) do not specifically refer to PVC tip culture and suggest systematic removal and culture of the catheter in case of suspected intravascular catheter-related bloodstream infection. Moreover, data regarding the proportion of PVC tip cultures performed in patients with suspected PVCRBSI are scarce, and when reported the proportion is frequently under 50% (18, 19). Given these findings, we may conclude that a systematic removal and culture of PVC should be performed not only in all patients with clinical apparent phlebitis but also in subjects with systemic signs of infection and without a known septic focus. Interestingly, the proportion of cases without phlebitis was higher in patients with Gram-negative PVCRBSI, as one-fifth of the patients did not have signs of local inflammation. Considering all this information, we may also infer that the actual incidence of Gram-negative PVCRBSI may be underestimated.

This study has several limitations. First, as a study from a single institution, the generalizability of our results is difficult; however, several reports from other centers also highlighted an increase in the incidence of Gram-negative infections. Second, the incidence rate in our study was estimated using the number of patient days as a reference unit as data regarding catheter days were not available. Indeed, knowing the actual number of days at risk would have been optimal to characterize the incidence of PVCRBSI in our population. Third, internationally validated criteria for the diagnosis of PVCRBSI are not currently available, and thus there is a risk of over- or underdiagnosis. Fourth, PVC tip culture was performed only in a minority of patients, possibly resulting in overdiagnosis of PVCRBSI (for example, in cases of chemical phlebitis). Nevertheless, we think that having an infectious diseases team dedicated to follow and review each patient ensured proper diagnosis and management. Finally, as already stated, given the relatively high number of patients who were diagnosed with PVCRBSI thanks to a positive tip culture in the absence of phlebitis (especially in the case of Gram-negative bacterial etiology), it is possible that the actual incidence rate of PVCRBSI may be higher than what we reported as cases of bacteremia of unknown focus without signs of phlebitis at the PVC insertion site might not have been considered possible PVCRBSI.

In conclusion, in our study we reported an increase in the incidence rate and prevalence of Gram-negative PVCRBSI. Remarkably, approximately one out of five patients with Gram-negative PVCRBSI did not show signs of phlebitis. PVC tip culture should be performed in all patients with suspected PVCRBSI and in patients with bacteremia without a clinically apparent focus, even in the absence of phlebitis. As PVCRBSI are common and potentially fatal, physicians need to maintain a high degree of suspicion in order to promptly diagnose and treat patients with this infectious complication.

MATERIALS AND METHODS

Study design. This study was a prospective observational study including all episodes of short-term peripheral venous catheter-related monomicrobial bacteremia diagnosed from January 1992 to December 2016 at the Hospital Clínic in Barcelona. Our center is a 700-bed tertiary university hospital covering an urban population of 550,000 inhabitants. The decision regarding the necessity and the type of short-term peripheral venous catheter was made by the patient's physician.

In our center, a dedicated team of infectious diseases physicians and microbiologists identifies and prospectively follows up all patients with bacteremia until death or 30 days after diagnosis, whichever occurs first. For each patient, a set of selected demographic, clinical, biochemical, microbiological, and antimicrobial treatment variables are collected and entered into a specific database.

Standard procedures of catheter insertion and management in our center were previously described (25). Peripheral catheter site and adequate functioning are inspected in each nursing shift or when otherwise needed, as in the case of apparent malfunctioning or due to patient complaints. Consequently, peripheral catheters are removed in the case of signs of complications or if no longer needed. Predefined scheduled changes of peripheral catheter are never included as a routine practice since the literature is

controversial regarding the potential benefits of this procedure (26). PVCRBSI incidence rate is defined as the number of episodes/1,000 patient days.

STROBE (27) recommendations were followed in order to strengthen the reporting of the study.

Definition of study variables. Since a consensus regarding the definition of PVCRBSI is lacking, we applied the currently accepted definition of catheter-related bloodstream infections (8). Thus, PVCRBSI was defined as the presence of one positive peripheral blood culture and a positive semiquantitative or quantitative catheter tip culture that grew the same microorganism found in the peripheral blood culture; in the absence of a positive catheter tip culture, patients were diagnosed with PVCRBSI when there were local signs of phlebitis and absence of other evident infectious foci. Specifically, in the case of bacteremia due to coagulase-negative staphylococci without an available catheter tip culture, at least two sets of positive blood cultures drawn from different venipuncture localizations were required to make a diagnosis of PVCRBSI. All the cases of PVCRBSI were reviewed and discussed by the dedicated team of infectious diseases physicians and microbiologists responsible for treating and following the patient throughout the hospital admission.

Phlebitis was defined as the presence of two or more of the following signs or symptoms on examination of the catheter insertion site: pain (either reported by the patient or tenderness elicited by palpation), erythema, swelling, purulence, and a palpable venous cord, as previously described (25). The following data at the time of bloodstream infection diagnosis were obtained for all patients and prospectively recorded in the registry: age, sex, admission date, date of catheter insertion and number of days of catheter *in situ*, preexisting comorbidities, McCabe score (28), and presence of an indwelling urinary catheter. Moreover, data regarding administration of immunosuppressive therapy (20 mg of daily prednisone or equivalent), surgery, or other nonsurgical invasive procedures and antibiotic use within the month preceding the bacteremia were collected. Active empirical antibiotic therapy was defined as a treatment started within the first 24 h of the index blood cultures, having *in vitro* activity against the bacteria isolated. The presence of the following clinical factors when the blood cultures were drawn was also documented: local signs of phlebitis, presentation with septic shock (defined according to previous guidelines [29]), and presentation with fever. Persistent bacteremia was defined as the presence of positive blood cultures after initiation of active antibiotic therapy.

Microbiological methods. Between 1992 and 1997, blood samples were processed by a Bactec NR-730 system (Becton-Dickinson Microbiology System) and incubated routinely for 7 days. The Bactec 9240 system (Becton-Dickinson Microbiology System) was adopted in 1998 and uses an incubation period of 5 days. PVC tip culture was performed using a roll-plate method with a semiquantitative culture as described by Maki et al. (30), followed by catheter tip culture in an enriched thioglycolate medium (BBL), with an incubation time of 72 h at 35°C.

Isolates were identified according to standard techniques, including the matrix-assisted laser desorption–ionization time of flight (MALDI-TOF) technique (since 2012). Antibiotic susceptibility was determined according to the recommendations of the CLSI or EUCAST guidelines available at the time of diagnosis. For statistical analysis, intermediate susceptibility was considered resistance.

Statistical analysis. Baseline characteristics were compared using a chi-square test or Fisher's exact test for categorical variables and Wilcoxon's rank sum test for continuous variables. A chi-square trend test was used to evaluate differences observed during the study period. A univariate logistic regression analysis was carried out to explore factors associated with Gram-negative etiology of PVCRBSI. A multivariate model was subsequently built by subjecting variables with a univariate P value of <0.20 to a backward stepwise logistic regression procedure. The calibration of the model was assessed by means of the Hosmer-Lemeshow goodness-of-fit test. The presence of collinearity was tested using the variance inflation factor (VIF) and tolerance. Interactions between variables were explored. A subgroup analysis was performed in patients with a positive PVC culture. Continuous variables are reported as median (interquartile range [IQR]); categorical variables are reported as frequency (percentage); logistic regression analysis results are reported as adjusted odds ratios (aOR) with 95% confidence intervals (95% CI). A two-tailed P value of <0.05 was considered significant. Statistical analysis was performed using SPSS, version 20.0 (IBM SPSS, Chicago, IL, USA).

Ethics. The study was approved by the local ethics committee (HCB/2017/1029). No informed consent was sought since this was an observational study and clinical care was not influenced.

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