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## Peripherally inserted central catheters: a hidden emerging cause of infection outbreaks

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Running title: PICCs: an emerging hidden cause of outbreak

Keywords: blood stream infection, hospital-acquired infection, bacteremia, mortality

### Conflicts of interest

The authors declare no conflicts of interest.

### Compliance with Ethic Requirements

All the methods were carried out in accordance with the European General Data Protection Regulation. The study is a retrospective analysis of patients' biological and registry data issued from the Hospital information system, which is an authorized health care data base. Access to the registry has been approved by an ethical review committee and recorded in the EGDP registry under N° RGPD/APHM 2019-73. The study was supervised by a person who was fully aware of the confidentiality

requirements.

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## **Abstract:**

In our institution, between January 2010 and December 2017, 15,140 peripherally inserted central catheters (PICCs) were inserted in 12,314 patients. Using times series analysis to evaluate the annual historical trend (AHT), we observed a significant increase in bloodstream infections (AHT: 24,  $p < 0.001$ ) and associated deaths (AHT: 3,  $P = 0.02$ ) in patient with PICCs. The risk of experiencing bloodstream infection was significantly higher in patients with PICCs (OR: 9.6, 95% CI: 9.08-10.18,  $P < 0.001$ ). To reduce PICC-related bloodstream infections and their related mortality, we believe that it is important to limit the overuse of PICCs and to implement a “NO-PICCs” policy, limiting the insertion of PICCs to situations without other available options.

## 1 **Introduction**

2           Peripherally inserted central catheters (PICCs) are central catheters that were first used in  
3 1975<sup>1</sup>. PICCs are catheters that enter the body through the skin (percutaneously) at a peripheral site,  
4 extending to the superior vena cava (a central venous trunk) and remaining in place (dwelling within  
5 the veins) for days or weeks (see picture). They are currently used in inpatients and outpatients for  
6 several indications, mainly for intravenous antibiotics, parenteral nutrition and chemotherapy <sup>2, 3</sup>.  
7 However, PICCs are associated with various complications, particularly thrombosis and bloodstream  
8 infections (BSIs) <sup>4-6</sup>.

9           Bloodstream infections are life-threatening conditions associated with high morbidity and  
10 hospital costs. Indeed, the United States' Centers for Disease Control and Prevention (CDC) estimates  
11 that 250,000 BSIs and 80,000 catheter-related bloodstream infections (CRBSIs) occur annually in the  
12 United States, classifying it as the 12<sup>th</sup> cause of death in 2007 <sup>7, 8</sup>. Moreover, associated costs are  
13 estimated in the US to range from \$7,288 to \$29,156 per episode <sup>9</sup>.

14           A previous study performed in our institution in 2013 found that 1,033 patients experienced  
15 healthcare-associated BSIs in the 48 hours following admission, leading to a mortality rate of 11% at  
16 15 days <sup>10</sup>. Globally, in the literature, the incidence of CRBSIs associated with PICCs ranges between  
17 0.5% and 12.7% <sup>11, 12</sup>.

18           PICCs have been used in the four University Hospitals in Marseille since 2007, and routine  
19 monitoring of BSIs in hospitalized patients with PICCs began in 2010. The aim of our study was to  
20 compare the BSI and mortality rates in patients who received PICCs compared to those in patients  
21 without PICCs who were hospitalized in our setting between 2010 and 2017.

## 22 **Materials and Methods**

23           We retrospectively studied the positive blood culture data from our hospital center  
24 (Marseille, France) between January 2010 and December 2017. During this period, PICC lines were  
25 inserted by the radiology department only. All PICCs were implanted by the same team

26 (interventional radiology), only by trained senior or senior-supervised residents following national  
27 protocols edited by the French society for hygiene with the use of alcohol-based antiseptic  
28 techniques. The recommended vein to use was the humeral vein. Maintenance of the PICC line was  
29 performed according to the nursing protocols in each department. We used single light catheters,  
30 but in 2011, a system was implemented with a pressure check valve, which has been reported to be  
31 associated with a lower risk of contamination and bacteremia<sup>13</sup>. We defined BSI events according to  
32 the CDC as at least two positive blood cultures growing with commensal bacteria (coagulase-negative  
33 *Staphylococci*, *Micrococcus* spp., *Corynebacterium* spp., *Propionibacterium acnes*, and *Bacillus* spp.),  
34 or at least one culture growing with pathogenic bacteria, without any cultures with the same  
35 bacterium from another kind of sample within a 14-day period. The BSI events were then  
36 deduplicated according to patient identity number, sampling date and bacterial identification and  
37 were cross-checked against the list of PICCs installed in our institution over the study period. We  
38 considered that a BSI occurred in a patient with a PICC if the date of insertion of the PICC was prior to  
39 the date of the BSI event. Finally, we checked whether patients who had experienced a BSI event had  
40 died in the next 30 days in our center.

41 All statistical analyses were performed using R software (The R Project, Auckland, New  
42 Zealand). Proportional comparisons were performed using Pearson's  $\chi^2$  tests, and odds ratios (ORs)  
43 and confidence intervals (CIs) were calculated to evaluate the risk associated with the compared  
44 conditions. Finally, linear models were built to analyze the annual historical trends (AHTs) (i.e., the  
45 annual trend in the mean number of patients in different conditions). Classic linear regression  
46 models were applied to estimate the trends in the annual mean number of patients, through years.  
47 The trends for each condition were defined as the estimated slopes of each model and tested to zero  
48 (no trends). P-values  $\leq 0.05$  were considered to be significant.

49 All the methods were carried out in accordance with the European General Data Protection  
50 Regulation. The study is a retrospective analysis of patients' biological and registry data issued from  
51 the Hospital information system, which is an authorized health care data base. Access to the registry

52 was approved by the DPC (data protection committee) of our institution APHM (Assistance publique  
53 des hôpitaux de Marseille) and recorded in the European General Data Protection Regulation registry  
54 under N° RGD/APHM 2019-73. The study was supervised by a person who was fully aware of the  
55 confidentiality requirements.

## 56 **Results**

57 Between January 2010 and December 2017, 15,140 PICCs were inserted in 12,314 patients.  
58 Globally, 11,890 BSI events occurred in 10,942 patients (1.08 BSI events per patient) (Table 1). The  
59 annual number of patients with BSI increased significantly over time (AHT=30, P =0.04) in parallel  
60 with an increase in the number of PICC-associated CRBSIs (AHT=24, p-value<0.001). The annual  
61 increase in the number of patients hospitalized in our setting, as well as the number of patients with  
62 BSIs, was not significant (AHT=12, p-value=0.98 and AHT=9, p-value=0.5, respectively). Interestingly,  
63 over the period, the number of installed PICCs did not increase significantly, but this was likely  
64 related to the decrease in the number of PICCs inserted during the last 2 years (AHT=12, P=0.7).  
65 When we considered the total number of CRBSIs occurring in patients with PICCs (1,477 BSI events,  
66 9.8% of all the PICCs used) and the total number of BSIs in patients without PICCs (10,413 BSI events),  
67 the calculated risk of experiencing a BSI was significantly higher in patients with PICCs (OR: 9.6, 95%  
68 CI: 9.08-10.18, p<0.001).

69 Over the period, 255 (21.4%) of the 1,265 patients with a PICC-related CRBSI and 1,410  
70 (14.4%) of the 9,798 patients with BSIs without PICCs died within the first 30 days of follow-up (Table  
71 2). The 30-day mortality rate associated with PICC-related CRBSIs increased significantly from 2010 to  
72 2017 (AHT= 3, p-value=0.02), while it did not increase for patients with BSIs without PICCs (AHT= 2, p-  
73 value=0.6). The risk of dying following PICC-related CRBSIs was 1.5-fold higher than that in patients  
74 with BSIs but without PICCs (OR: 1.5, 95% CI: 1.30-1.74, p-value <0.001).

75 **The main microorganisms associated with BSIs were coagulase-negative Staphylococci**  
76 **(46.51%), followed by Enterobacteriaceae (23.25%), and *Staphylococcus aureus* and *Enterococcus spp***

77 (11.24% and 5.42%, respectively). No correlation was established between microbiology and  
78 mortality<sup>14</sup>.

## 79 Discussion

80 This time series study revealed an increasing number of BSIs among patients with PICCs, with  
81 a global 9.6-fold higher risk of BSIs in this population. Moreover, we identified that BSIs due to PICCs  
82 were associated with a risk of death that was 1.5 times higher than the risk in patients experiencing  
83 BSIs without PICCs. While patients with PICCs might have greater comorbidity rates, which were not  
84 recorded in this study (especially cancer), the increasing use of PICCs is particularly concerning,  
85 especially that it is known that in the US, approximately 41,000 BSI events occur each year in  
86 hospitalized patients carrying a central venous catheter<sup>7</sup>. A national French survey performed in  
87 2012 and 2017 identified an increase (+ 169%, range: 0.38 % to 1.3% (95% CI [1,59-3.31])) use of PICC  
88 lines compared to the use of other catheters<sup>15, 16</sup>. Of 1,620 patients who had experienced at least  
89 one hospital-acquired bloodstream infection, 3.4% of cases occurred in patients carrying PICCs<sup>16</sup>. In  
90 our study, an infection control intervention in 2014 may have resulted in a decrease in PICC insertion,  
91 followed by a nonsignificant trend of PICC-related CRBSI reduction.

92 In France, PICCs are especially indicated in outpatients and neonates who need venous  
93 access for more than seven days and less than three months. In our experience, because they are  
94 more easy to manipulate (interventional radiology) than other central venous catheters such as port-  
95 a-cath®, PICCs are often inserted for unjustified reasons such as to provide the following: prolonged  
96 antimicrobial therapy when an oral option is available, easy access for regular blood sampling,  
97 rehydration in elderly patients when subcutaneous infusion is feasible and, in the worst situation, for  
98 no reason (“just in case”). Moreover, PICCs are not regularly removed as soon as indicated (after the  
99 end of antimetabolic or antimicrobial chemotherapy), leading to late and life-threatening infectious and  
100 thromboembolic complications. Sengupta *et al.* found an increased risk of central-line-associated  
101 bloodstream infections of 33% per day after day 36 of PICC insertion<sup>17</sup>. To reduce BSIs and,  
102 subsequently, mortality associated with PICCs, we believe that it is important to limit the overuse of



103 PICCs and to implement a “NO-PICCs” policy, limiting the insertion of PICCs to situations where other  
104 options are not possible. In these situations, the risk of infectious complications (e.g., patient factors:  
105 neutropenia, hematologic diseases or other underlying conditions; and device factors: number of  
106 prior PICC insertions, number of lumens and duration of PICC placement, right-sided line insertion)  
107 should be taken into consideration <sup>2</sup>. Finally, central catheter-care practice bundles should be  
108 implemented, including regular staff training for correct insertion practices, appropriate handling of  
109 and maintaining a central line, and the importance of promptly removing unnecessary PICCs. This can  
110 be achieved by using either innovative electronic tools <sup>18</sup> or new management approaches such as  
111 designated nursing teams <sup>19</sup>. Similarly, to address the electronic monitoring of hygiene and  
112 surveillance systems, new approaches to enhance the traceability of catheters are being developed,  
113 with the goal of helping caregivers monitor catheter duration and force catheter removal as soon as  
114 possible <sup>20, 21</sup>.

115           Although there are limitations to our study (particularly the fact that we were unable to  
116 assess the CRBSI incidence per day of PICC use due to a lack of data), our results underlined the  
117 importance of reconsidering the use of PICCs in hospital settings and of infection prevention. Our  
118 study also highlights the need to perform case-control studies to better evaluate the incidence and  
119 mortality rate of bloodstream infections in patients with PICCs as well as in those with implantable  
120 ports and peripheral venous access devices.

Figure: The PICC line enters the body through the skin (percutaneously) at a peripheral site, extends to the superior vena cava (a central venous trunk), and stays in place (dwells within the veins) for days or weeks.

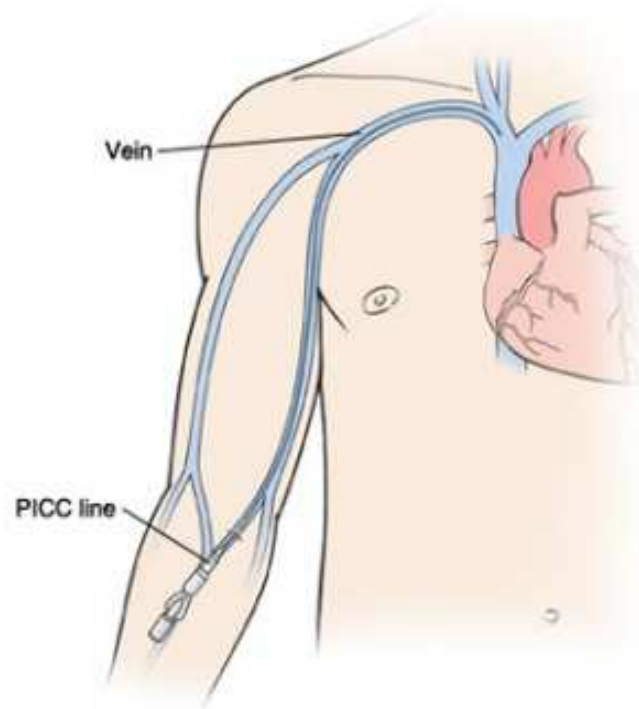


Table 1: Annual historical trends (AHTs) of **number of patients with bloodstream infections** with and without PICCs over 7 years of follow-up (2010-2017).

Years	No. of hospitalized patients	No. of installed PICCs		BSIs <sup>1</sup> with PICCs		BSIs without PICCs		Total		P-value *	OR (95% CI)
		No. of patients	No. of events	No. of patients	No. of events <sup>2</sup>	No. of patients	No. of events	No. of patients	No. of events		
2010	114,171	1,293	1,638	78	88	1,263	1,308	1,341	1,396	<0.01	4.8 (3.87-6.03)
2011	120,893	1,520	1,902	99	112	1,248	1,314	1,347	1,426	<0.01	5.6 (4.59-6.83)
2012	120,339	1,529	1,884	121	135	1,174	1,254	1,295	1,389	<0.01	7.2 (6.00-8.67)
2013	121,806	1,605	1,959	129	151	1,097	1,167	1,226	1,318	<0.01	8.5 (7.13-10.13)
2014	120,498	1,751	2,128	171	195	1,170	1,236	1,341	1,431	<0.01	9.6 (8.17-11.19)
2015	118,427	1,769	2,144	200	237	1,284	1,391	1,484	1,628	<0.01	10.3 (8.88-11.87)
2016	117,664	1,577	1,946	249	297	1,259	1,320	1,508	1,617	<0.01	15.6 (13.64-17.86)
2017	117,626	1,270	1,539	218	262	1,303	1,423	1,521	1,685	<0.01	16.5 (14.33-19.07)
<b>Total</b>	951,424	12,314	15,140	1,265	1,477	9,798	10,413	11,063	11,890	<0.01	9.6 (9.08-10.18)
<b>AHT (p-value)</b>	12 (0.98)	12 (0.7)		24 (p<0.01)		9 (0.5)		30 (0.04)			

<sup>1</sup> BSI: blood stream infection

<sup>2</sup>Event is the number of PICCs. The number of PICCs can be larger than the number of patients

No.: number; OR: odds ratio; CI: confidence interval; AHT: Annual historical trend

\* Uncorrected bilateral  $\chi^2$  tests, odds ratios (ORs), confidence intervals and AHTs were calculated using R. P-values  $\leq 0.05$  were considered statistically significant. Comparisons were made between N° events of BSI

AHT: annual historical trends

AHTs were calculated using linear models, with each value demonstrating the annual trend of the mean number of patients in the different conditions.

Table 2: Annual historical trends (AHTs) of **30-day mortality in patients with bloodstream infections** with and without PICCs over 7 years of follow-up (2010-2017). AHTs were calculated using linear models, with each value demonstrating the annual trend of the mean number of patients in the different conditions. p-values  $\leq 0.05$  were considered to be significant.

Years	Total No. of deaths	With PICCs		Without PICCs		P-value *	OR (95% CI)
		No. alive at 1	No. dead at 1	No. alive at 1 month	No. dead at 1		
2010	2,651	57 (78.1%)	21 (26.9%)	1,060 (83.9%)	203 (16.1%)	0.01	1.9 (1.14-3.24)
2011	2,593	68 (68.7%)	31 (31.3%)	1,096 (87.8%)	152 (12.2%)	<0.01	3.3 (2.08-5.19)
2012	2,719	100 (82.6%)	21 (17.4%)	1,003 (85.4%)	171 (14.6%)	0.4	1.2 (0.75-2.03)
2013	2,858	97 (75.2%)	32 (24.8%)	9,380 (85.5%)	159 (14.5%)	<0.01	1.9 (1.26-3.00)
2014	2,694	146 (85.4%)	25 (14.6%)	1,008 (86.2)	162 (13.8%)	0.8	1.1 (0.68-1.68)
2015	2,812	165 (82.5%)	35 (17.5%)	1,099 (85.6%)	185 (14.4%)	0.3	1.3 (0.85-1.87)
2016	2,842	201 (80.7%)	48 (19.3%)	1,069 (84.9%)	190 (15.1%)	0.1	1.3 (0.95-1.91)
2017	2,946	176 (80.7)	42 (19.3%)	1,115 (85.6%)	188 (14.4%)	0.1	1.4 (0.98-2.05)
Total	22,115	1,010 (78.6%)	255 (21.4%)	8,388	1,410 (14.4%)	<0.01	1.5 (1.30-1.74)
AHT (p-value)	41 (<0.01)	21 (<0.01)	3 (0.02)	7 (0.5)	2 (0.6)		

No.: number; OR: odds ratio; CI: confidence interval; AHT: annual historical trend

\* Uncorrected bilateral  $\chi^2$  tests, odds ratios (ORs), confidence intervals and AHTs were calculated using R. P-values  $\leq 0.05$  were considered statistically significant.

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