UNIL | Université de Lausanne
Faculté de biologie et de médecine

CHUV

Mémoire de Maîtrise en médecine No 890

Bloodstream infections related to totally implantable venous access port: What is the situation in our hospital?

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Lausanne, décembre 2012

Abstract

Port-a-Cath© (PAC) are totally implantable devices that offer an easy and long term access to venous circulation. They have been extensively used for intravenous therapy administration and are particularly well suited for chemotherapy in oncologic patients. Previous comparative studies have shown that these devices have the lowest catheter-related bloodstream infection rates among all intravascular access systems. However, bloodstream infection (BSI) still remains a major issue of port use and epidemiology data for PAC-associated BSI (PABSI) rates differ strongly depending on studies. Also, current literature about PABSI risk factors is scarce and sometimes controversial. Such heterogeneity may depend on type of studied population and local factors. Therefore, the aim of this study was to describe local epidemiology and risk factors for PABSI in adult patients in our tertiary-care university hospital.

We conducted a retrospective cohort study in order to describe local epidemiology. We also performed a nested case-control study to identify local risk factors of PABSI. We analyzed medical files of adult patients who had a PAC implanted between January 1st, 2008 and December 31st, 2009 and looked for PABSI occurrence before May 1st, 2011 to define cases.

Thirty nine PABSI occurred in this population with an attack rate of 5.8%. We estimated an incidence rate of 0.08/1000 PAC-days using the case-control study. PABSI causative agents were mainly Gram positive cocci (62%). We identified three predictive factors of PABSI by multivariate statistical analysis: neutropenia on outcome date (Odds Ratio [OR]: 4.05; 95% confidence interval [CI]:1.05-15.66; p=0.042), diabetes (OR: 11.53; 95% CI: 1.07-124.70; p=0.044) and having another infection than PABSI on outcome date (OR: 6.35; 95% CI: 1.50-26.86; p=0.012). Patients suffering from acute or renal failure (OR: 4.26; 95% CI: 0.94-19.21; p=0.059) or wearing another invasive device (OR: 2.99; 95% CI: 0.96-9.31; p=0.059) did not have a statistically increased risk for developing a PABSI according to classical threshold (p<0.05) but nevertheless remained close to significance.

Our study demonstrated that local epidemiology and microbiology of PABSI in our institution was similar to previous reports. A larger prospective study is required to confirm our results or to test preventive measures.

Key words: port, bloodstream infection, intravascular device

Note préliminaire: il a été convenu avec le tuteur que mon travail d'écriture consisterait à produire un article possiblement publiable. Partant de ce principe, certaines images tirées d'autres études ont été ajoutées pour le travail de master mais ne feraient pas partie d'une éventuelle publication. Elles sont indiquées par un « S. » pour « supplementary » devant la légende de figure ou de table.

Introduction

Totally implantable venous access port (or Port-a-Cath©, named PAC thereafter) are intravascular devices that provide an easy and permanent access to large veins. They have been introduced since the early 1980s and are now largely used in oncology patients who require long term chemotherapy with repeated venous punctures. These devices are also well suited for delivery of other therapies such as parenteral nutrition, blood transfusion or intravascular fluids (1). The number of PACs implanted annually in the USA has been estimated as more than 5 millions in 2000 (2) and must be even higher nowadays.

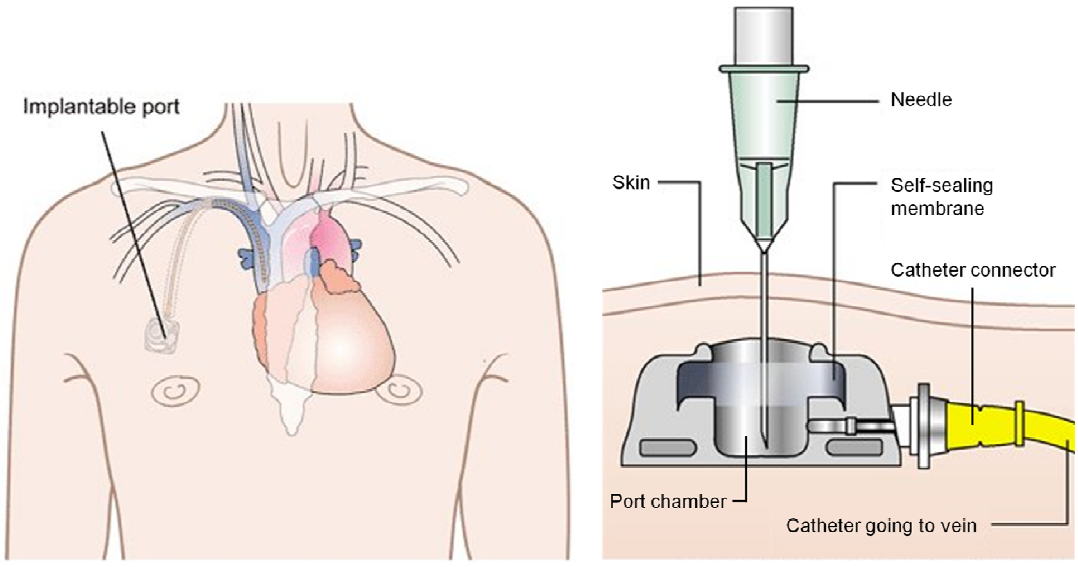
PACs are composed of a subcutaneous chamber with a self-sealing membrane that can be accessed by a needle through the intact skin and are connected to a central venous catheter. The device is surgically inserted beneath the skin under local anesthesia. The preferred implantation site is below the right clavicle in order to access the superior vena cava through the subclavian or the internal jugular vein (3) (see

S. Figure 1).

S. Figure 1 : Scheme of Port-a-Cath© insertion site and components

Left: Port-a-Cath© insertion site under right clavicle with catheter access to right subclavian vein and superior vena cava.
Right: front view of Port-a-Cath© implanted beneath skin and punctured.

Modified from www.cancerhelpuk.org



PACs have several advantages for long term use compared to other central venous catheters. First, they are more comfortable for patients as they require less nursing (catheter changing, flushing…), are less visible and are less impeding for daily life activities such as showers or swimming. Moreover,

their access to large vessels allows rapid dilution of potentially toxic infusates such as chemotherapy and thus minimizes venous damages (1).

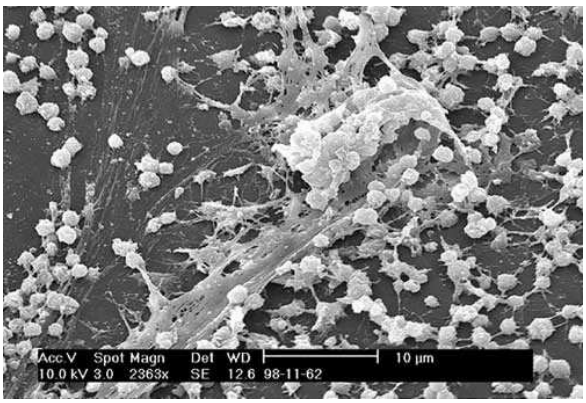
In a large comparative review (4), PACs had the lowest catheter-related bloodstream infection (CRBSI) rates among all intravascular access systems. However, bloodstream infection (BSI) still remains a major issue of port use and epidemiology data for PAC-associated BSI (PABSI) rates differ strongly depending on studies (see Table 1). Other complications include short-term complications related to surgery and long-term complications such as port-related venous thrombosis, catheter occlusion or catheter fragmentation (1,5).

Table 1 : Epidemiology data for Port-a-Cath©-associated bloodstream infections from different studies.

Data come from some recent studies focusing on Port-a-Cath© systems and are compared together without concern for studied population. Research type is also detailed.

Reference	Type of study	Attack rate	Incidence rate
Chang et al. (6)	Retrospective	8.9%	0.26/1000 catheter-days
Dal Molin et al. (7)	Prospective	-	0.04/1000 catheter-days
Maki et al. (4)	Review of 17 studies	3.6-4.0%	0.2/1000 catheter-days
Sakamoto et al. (8)	Prospective	1.4%	-
Teichgräber et al. (9)	Retrospective	5.1%	0.145/1000 catheter-days
Touré et al. (10)	Prospective	13.0%	0.76/1000 catheter-days
Yoshida et al. (11)	Retrospective	-	2.81/1000 days of use

The general mechanism of intravascular devices colonization by microorganisms is achieved by biofilm formation on synthetic material and dissemination of free-floating forms along the catheter (see S. Figure 2). Colonization can occur already 24h after device insertion (12). For PACs, the main sources of infection are thought to be intraluminal colonization of the chamber during iterative injections and extraluminal colonization by skin flora from patient or medical staff. This second mechanism is believed to be less frequent in long term infections since PACs are inserted beneath intact skin (13). Contamination of administrated infusate is also a rare possibility. PAC infection can remain local and cause a subcutaneous pocket infection at implantation site or eventually spread to bloodstream and become systemic (14). Using ROC curves in a retrospective study, Yoshida et al. determined that the safety cutoff before PABSI was 33 utilization-days (11). The main microorganisms responsible for PAC infections are *Staphylococcus epidermidis* and other coagulase-negative staphylococci, *Staphylococcus aureus* and Candida species (14). Gram-negative bacilli are also causative agent of nosocomial PABSI (15).



S. Figure 2 : Scanning electron micrograph of a *Staphylococcus* biofilm on the inner surface of a needleless connector. Photograph by Janice Carr, Centers for Disease Control and Prevention, Atlanta, GA USA. www.cdc.gov

Once a PABSI is suspected empirical antibiotic therapy is prescribed depending on the likely pathogen, severity of patient's illness and patient co-morbidities. It is then adapted to the cultured pathogen. Duration of treatment and decision between PAC removal or salvage depend on PABSI complications and causal pathogen. In general, PAC can be retained in uncomplicated coagulase-negative staphylococci, enterococci and some Gram-negative bacilli infections (17).

According to Raad et al. (15), BSI related to intravascular devices have an estimated attributable mortality ranging from 12% to 25% in critically ill patients, although this point remains controversial (14). To our knowledge, no attributable death has been reported for PABSI, but this point has been only little assessed. Complications of PABSI result in an increased morbidity. These include severe sepsis or septic shock, infectious metastasis (infectious endocarditis, septic arthritis, osteomyelitis, organ abscess), PAC removal with potential therapy delay or cancelling (13). Biffi et al. (18) have estimated an averaged increased cost related to PABSI ranging from $1145 to $2141 per patient.

According to IDSA guidelines, classical risk factors for catheter-related BSI comprise *the type of intravascular device, the type of and intended use for the catheter, the insertion site, the experience and education of the individual who installs the catheter, the frequency with which the catheter is accessed, the duration of catheter placement, the characteristics of the catheterized patient, and the use of proven preventative strategies* (17). Studies focusing on PABSI predictive factors found in the literature are scarce and sometimes controversial. The cumulative number of utilization-days significantly increases the risk of PABSI. Patients who receive parenteral nutrition have been shown to have significantly higher rates of PABSI than with other uses. Palliative care administered immediately after PAC implantation also correlates with increased PABSI. The significant factors of patient's condition that have been identified are neutropenia and preexisting sepsis. The type of primary illness may play a role as well, since colorectal and pancreatic cancers are thought to increase the risk of PABSI compared to other primary malignancy sites. On the other hand, types of port system or insertion site localizations (arm vs. subclavian) are not associated with significantly different rates of infection (3,4,6,7,11,19–21).

Some of these potential risk factors are still debated and need further evidence. Also, research concentrating on PAC-carrying populations may not define the same predictive factors for BSI than previous studies on other catheter types. Moreover and as already shown above, reported epidemiology data is inconsistent. Some reviews show even important variations in incidence ranges without further precision (Kurul et al. : 2.4-16.0% (3); Jordan et al. : 2.6-27% (5); Biffi et al. : 0-22% (18)). This variability could be explained by definition heterogeneity of PABSI and differences in studied populations or even by differences in local management of risk factors and prevention strategies implementation. Currently, there is no data on PABSI epidemiology and local risk factors available in our institution. The aim of this study was thus to describe local epidemiology and risk factors for PABSI in adult patients in a tertiary-care university hospital. This could help our institution and others to better prevent PABSI and decrease related morbidity.

Patients and methods

We conducted a retrospective cohort study in a 1020-bed tertiary care university hospital in Switzerland. We included all patients aged more than 18 who had a PAC implanted between January 1st, 2008 and December 31st, 2009 according to the operation theatre statistics. End of follow-up for the whole cohort was set on May 1st, 2011.

This study was approved by our local research ethics comity (*Commission cantonale d'éthique de la recherche sur l'être humain,* Lausanne, Switzerland).

Attack rate and definition of PABSI

In order to calculate the attack rate of PABSI, we looked for positive blood cultures in included patients from January 1st, 2008 to May 1st, 2011 in the microbiology information system. We considered only the first case of PABSI for each patient. Since no universal definition of PABSI has been established yet, we based our definition criteria on different guidelines (14,17,22) and adapted them to available data in the electronic files, especially in the infectious diseases consilium report when available (see Table 2).

Table 2 : Minimal microbiological criteria for definition of Port-a-Cath©-associated bloodstream infection

In all situations presented below, the bloodstream infections was considered while a Port-a-Cath© (PAC) was implanted and had no other apparent source than the PAC. Microorganisms of the same species collected from separate blood cultures and having the same antibiotic susceptibility profile were considered as belonging to the same strain.

PAC: Port-a-Cath©; PABSI: PAC-associate bloodstream infection

	Blood cultures yielding a common skin contaminant[1]	**Blood cultures yielding other results**
Possible PABSI	≥ 2 sets of blood cultures drawn from the PAC yielding the same bacterial strain OR Positive culture of 1/1 set drawn from the PAC AND presence of fever not explained otherwise.	Positive culture of ≥ 1 set of blood culture drawn from the PAC
Probable PABSI	≥ 2 sets of blood cultures, with at least one drawn from a peripheral vein, yielding the same bacterial strain	Positive culture of ≥ 1 set of blood culture drawn from a peripheral vein
Definite PABSI	Probable PABSI[2] confirmed by a PAC culture that yielded the same pathogen.	

[1] Including diphteroids, *Bacillus* spp., coagulase-negative staphylococci and micrococci

Features of PABSI

The *first day of PABSI* was defined as the date of the first PABSI-defining blood culture. The *time to PABSI* was defined as the time elapsed between the PAC implantation and the first day of PABSI. The *duration of PABSI* was defined as the time elapsed from the first day of PABSI and the first day with complete culture negation when available, or the day of end of symptoms or death.

A hospital-onset PABSI was defined as a PABSI occurring 48 hours or more after hospital admission. A local PAC infection was suggested by the presence of typical inflammatory signs (redness, swelling, pain, purulent exsudate) at the PAC implantation site. We used the criteria of Annane et al (23) to define septic syndrome.

We defined PABSI complications as PAC removal, metastatic infectious focus, transfer to ICU or death when they were a direct consequence of PABSI. Deaths were reported in both populations if they occurred between the implantation date and 15 days after the outcome date; this endpoint was chosen in order to include deaths probably attributable to PABSI in the case group.

Risk factors

The risk factors for developing a PABSI were analyzed using a nested case-control study.

We defined controls as adult patients who had a PAC implanted during the study period and who did not develop a PABSI until the end of follow-up. For each PABSI case of the cohort, we selected the control patient who had the closest implantation date, and who had medical information available on a reference date which was set on the date of the PABSI for the corresponding case plus or minus 90 days. Reference dates in controls as well as dates of PABSI in cases are called *outcome dates* thereafter. Control patients were excluded when their PAC was removed before the respective outcome date, and replaced by the next most suitable control. Follow-up time was defined as the time from implantation to PABSI in cases and as the time from implantation to death, PAC removal or end date of follow-up in controls.

We looked for an association of PABSI with the following covariates documented on outcome dates: PAC in use (defined as the performance of nursery care such as needle or dressing change), presence of another invasive device, anemia (hemoglobin lower than 130 g/L for men or lower than 120 g/L for women), neutropenia (counts lower than 1800 neutrophils/µl), thrombocytopenia (counts less than 150 G/L), overweight (body mass index higher than 25.0 kg/m^2), history of smoking or history of alcohol abuse, diabetes mellitus of both types, renal failure and concomitant infection. We also recorded any medical condition mentioned in patient history. We also collected date about chemotherapy, radiotherapy and glucocorticoids or antacids administrations within 30 days before the outcome date.

Statistical analyses

We analyzed our data using STATA® 12.0 software (StataCorp, College Station, TE). We compared covariates using Fisher's exact test for categorical variables, and Student's t-test for continuous variables. Covariates associated with PABSI at a p-level of 0.2 or less were candidates for the building of a multivariate logistic regression model. We then tested all covariates not retained in the model for possible confounding.

Results

Between January1st, 2008 and December 31st, 2009, a total of 670 PACs were implanted in 654 patients. Thirty-nine PABSI were detected in our study population representing an attack rate of 5.8%. This diagnosis was referred as possible in 19 patients (49%), as probable in 16 patients (41%) and as definite in 4 patients (10%). Sixty-nine other patients had positive blood cultures in the microbiology database but did not meet the PABSI criteria. The depicted flow-chart of this study is presented in Figure 1. Median time to PABSI was 179 days (range 1-1045). Curve of time-to-event analysis for PABSI occurrence in cases is shown in Figure 2

Microbiology results of blood cultures are shown in Table 3.

Clinical characteristics of PABSI are summarized in Table 4. Twenty-nine patients had complications following infection (74%), which are further detailed in the table. Death was clearly attributable to PABSI in one case, whereas PABSI possibly contributed to death in 6 other cases.

Figure 1 : Study flow chart

PAC: Port-a-Cath© PABSI: Port-a-Cath©-associated bloodstream infection

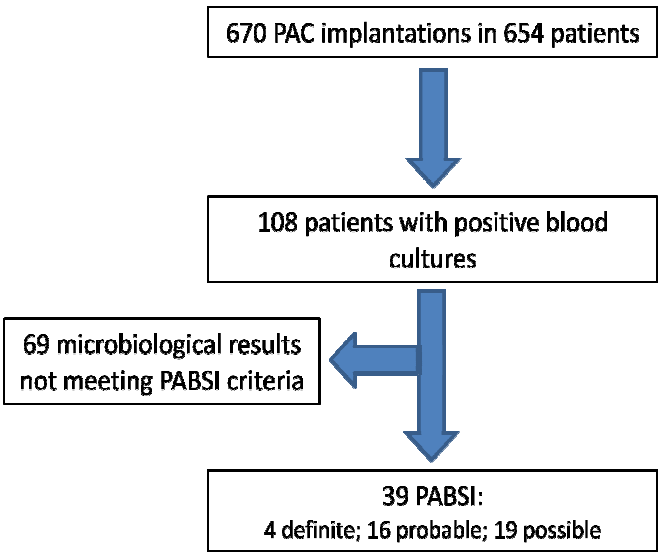


Figure 2 Time to Port-a-Cath©-associated bloodstream infection analysis

Cumulative PABSI-free estimate over time illustrated by Kaplan-Meier time-to-event analysis

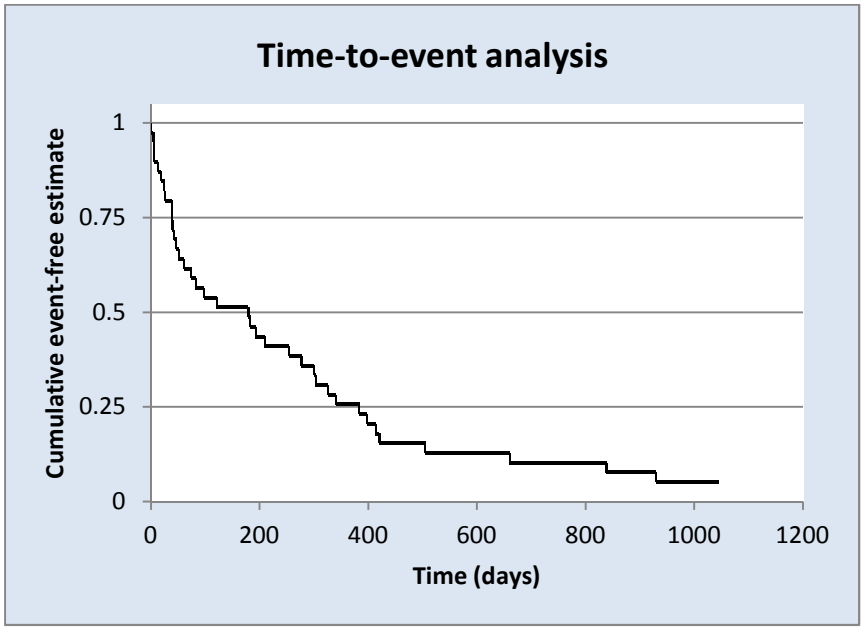


Table 3 : Distribution of pathogens isolated from blood cultures in the Port-a-Cath©-associated bloodstream infection group

Microorganisms	N	%
Gram-positive cocci	**24**	**61.5**
Coagulase-negative staphylococci	14	35.9
Staphylococcus aureus	6	15.4
Enterococcus spp	3	7.7
Finegoldia mana	1	2.6
Gram-negative bacilli	**9**	**23.1**
Enterobacter spp	4	10.3
Klebsiella pneumoniae	1	2.6
Pseudomonas fluorescens	1	2.6
Stenotrophomonas maltophilia	1	2.6
Escherichia coli	1	2.6
Proteus mirabilis	1	2.6
Gram-positive bacilli	**2**	**5.1**
Listeria monocytogenes	1	2.6
Achromobacter xylosoxidans	1	2.6
Candida albicans	**1**	**2.6**
Mixed flora	**3**	**7.7**

Table 4 : Clinical characteristics of Port-a-Cath©-associated bloodstream infection

Cumulative counts and percentages of cases presenting each characteristic are shown. *PABSI: Port-a-Cath©-associated bloodstream infection*

Periods related to PABSI	Days	Range
Median time to PABSI	179	1-1045
Median duration of PABSI	4	1-36
Median duration of antibiotic therapy	13	0-42

Infections characteristics	N	%
Hospital onset	24	61.5
Local infection signs	6	15.4
Septic syndrome diagnosis	16	41.0
Sepsis	11	28.2
Severe sepsis	4	10.3
Septic shock	1	2.6

Complications of PABSI	N	%
Cases with complications	29	74.4
PAC removal	23	59.0
Infection secondary spread	3	7.7
Cardiac decompensation	2	5.1
Transfer to ICU	4	10.3
Attributable death	7	17.9
Definite	1	2.6
Possible	6	15.4

Nested case-control study

Median follow-up time of our case-control study was 406 days per PAC (range: 1-1213) for a total time of 38'982 days. Descriptive data of the study groups are shown in Table 5. Time-to-event analysis for PAC maintaining in both groups is illustrated in Figure 3. Results of unilateral statistical analysis for PABSI potential risk factors are presented in Table 6.

Figure 3 : Time to Port-a-Cath© removal analysis in cases and controls groups

Cumulative probability of PAC maintaining over time in cases (red line) and controls (black line) illustrated by Kaplan-Meier time-to-event analysis is shown.

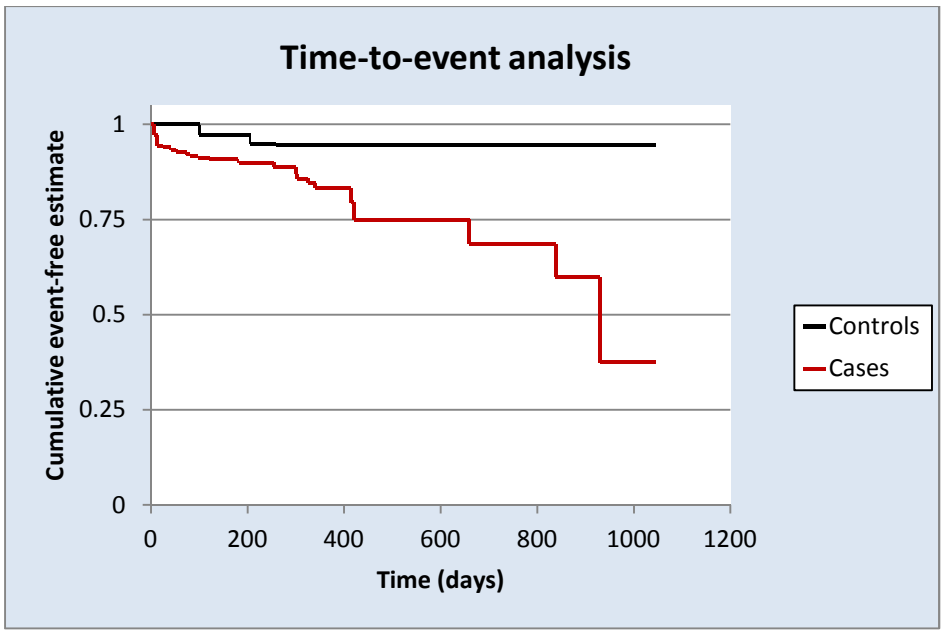


Table 5 : Descriptive characteristics for both groups

Cumulative counts of patient presenting condition in each group are shown. P-values were calculated by Fisher's exact test for categorical variables, and Student's t test for continuous variables. *PAC: Port-a-Cath©; CRF: Chronic renal failure.*

Covariates	Cases	Controls	P value
Patients number	39	39	
Sex (M/F)	21/18	17/22	0.820
Mean age, years (range)	59 (22-84)	58 (29-77)	0.592
Deaths during PAC carriage	10	7	1.000
PAC removal	23	3	<0.001
Mean hospital stay, days (range)	42 (0-209)	9 (0-48)	<0.001
Reason for PAC use			
Chemotherapy	37	38	1.000
Solid tumor	30	33	1.000
Hematological malignancy	7	5	1.000
Nutrition	-	1	1.000
Vascular access in CRF	2	-	1.000

Table 6 : Univariate analysis results for potential risk factors.

Cumulative counts and proportion of patient presenting the following conditions in each group and results of statistical comparisons are shown for unilateral 2-sided Fisher's exact test. *PAC: Port-a-Cath©*

Potential risk factors	Cases, n (%)	Controls, n (%)	P value
PAC in use on outcome date	32 (82.1)	20 (66.7)	0.019
Anemia	38 (97.4)	31 (79.5)	0.029
Neutropenia	12 (31.6)	5 (12.8)	0.058
Thrombocytopenia	14 (35.9)	9 (23.1)	0.321
Diabetes	5 (12.8)	1 (2.6)	0.200
Overweighted	24 (61.5)	24 (61.5)	1.000
History of smoking	11 (31.4)	17 (50.0)	0.145
History of alcohol misuse	10 (27.0)	7 (18.9)	0.581
Renal failure	10 (25.6)	3 (7.7)	0.065
Other infection	14 (35.9)	3 (7.7)	0.005
Recent chemotherapy	25 (64.1)	25 (64.1)	1.000
Recent radiotherapy	10 (25.6)	7 (18.0)	0.584
Recent use of glucocorticoids	10 (25.6)	5 (12.8)	0.250
Use of antacids	22 (56.4)	15 (38.5)	0.173
Other invasive device	17 (43.6)	10 (25.6)	0.153

Multivariate analysis

Nine potential risk factors were retained for multivariate modeling and were compared for confounding effects. This analysis yielded three independent predictive factors for PABSI that were statistically significant (p-value<0.05). Two other factors were close to significance (p-value<0.06) and were also included in the final model (see Table 7).

Table 7 : Multivariate analysis of potential risk factor for PAC-associated bloodstream infections

These results were obtained by multivariate logistic regression model. Odds ratios are shown with 95% confidence interval (95% CI) and p-values. ** P-value <0.05*

Potential risk factors	Odds Ratio	95% CI		P-value
Neutropenia	4.05	1.05	15.66	0.042*
Diabetes	11.53	1.07	124.70	0.044*
Other infection	6.35	1.50	26.86	0.012*
Renal failure	4.26	0.94	19.21	0.059
Other invasive device	2.99	0.96	9.31	0.059

Discussion

We conducted a retrospective study to investigate local epidemiology and risk factors of PABSI in our university tertiary-care hospital. According to current evidence, PACs have the lowest bloodstream infection rates among intravascular devices (4,14,17,22). In this cohort, 39 patients developed a PABSI on 670 PAC implantations, thus representing an attack rate of 5.8%. Assuming that mean follow-up time in control group is representative of the remaining cohort, we estimated an incidence rate of 0.08/1000 PAC-days. Although, available data is inconsistent in literature, our results are similar to previous studies (4,6–11) (see Table 1). Compared to these studies, our attack rate is in the middle range (1.4-13%), while our extrapolated incidence rate is in the lower values (0.04-0.76/1000 catheter-days). We possibly had a longer follow-up time in our case-control study than in these reports. As shown by Kaplan-Meier time-to-event analysis, PABSI's probability is high at the beginning of PAC carriage (see Figure 2). In fact, the median time to PABSI in our study is 179 days which represents 17% of our longest time to PABSI (1045 days). This agrees with other reports which showed that risk of PABSI decreases over time of catheterization (3) and that intravascular devices are rapidly colonized after implantation (12).

Pathogen epidemiology for PABSI depends on local community and hospital flora, type of studied population, type of intravascular catheter and type of PAC's use (14,15,22,24). Nevertheless, our findings are consistent with current reviews as the first isolated causative agents of PABSI were coagulase-negative staphylococci (36%) and *Staphylococcus aureus* (15%). We found a relatively high proportion of Gram-negative bacilli (23%) that may be a consequence of a high proportion of hospital-onset PABSI in our population (61%); in fact, 8 patients over 9 hospital-onset PABSI were infected by Gram-negative bacilli among which we retained 3 possible, 3 probable and 2 definite diagnosis of PABSI (data not shown). This is in line with a previous report (25). We recorded only one candidemia (2.6%) which corroborates expected proportion (24).

Complications of PABSI occurred in 29 cases (74%). In cases group, PAC was removed in 23 patients (59%) and was always ablated because of PABSI. Thus, PABSI was the cause of the significantly higher number of PAC extractions in cases compared to controls ($p<0.001$). This is further illustrated by Kaplan-Meier analysis (see Figure 3) with a 0.5 cumulative probability of PAC removal after 930 days in cases and a maximal cumulative probability of 0.94 after 1045 days in controls. Since PABSI caused an earlier PAC removal in cases, it may have caused a prejudice in this group, especially in pre-established therapy program. Moreover, among patients who had their PAC removed, 20 cases and 2 controls were utilizing their PAC on outcome date (87% and 67%, respectively). Nevertheless, PACs were replaced only in 2 patients before the end of follow-up and we do not know reasons for not implanting new PACs in others (patient's health state or refusal, no more utility of PAC, change in therapy program…). Therefore, we cannot conclude whether removal yielded to greater morbidity.

PABSI was responsible for secondary infection spread in 3 cases (7.7%), cardiac decompensation in 2 cases (5.1%) and transfers to ICU in 4 cases (10.3%), which certainly generated extra care and costs. On 10 deaths reported in the cases' group, PABSI was responsible for one death and contributed to death of 6 other patients. The cumulative count of deaths in case group was not statistically different

than in control group, though. If we consider that the control group is a representative sample of the whole cohort, our study would therefore show no increased mortality related to PABSI in agreement with other studies on intravascular devices (14).

We performed a nested case-control study without pair matching other than similar time to PABSI in cases and to an analogous date in controls. Since this represents an artificial matching, it is reasonable to accept that the control group was generated randomly and is thus representative of the whole cohort. In a recent study, Touré et al. (10) excluded PABSI occurring before day 14 after catheter insertion from their analysis in order to eliminate catheter contamination at time of insertion. As previously mentioned, catheter colonization is present as early as 24h after insertion (12). Since we matched cases and controls on similar time to outcome, we decided to include early PABSI as well in our study groups. This situation occurred in 5 cases (range: 1-13 days) and 5 controls (range: 5-13 days)

The population of the case-control study turned out to be mainly composed of patients with solid malignancies (77% in cases versus 84% in controls) and PACs were mainly used for chemotherapy injections (95% in cases versus 97% in controls). Both populations were then not different in terms of type of PAC use and underlying diseases. Consequently, we did not find any correlation between these factors and PABSI. This is inconsistent with current literature since hematological malignancies are considered as a risk factor for CRBSI (3). To our knowledge, this factor was never assessed for PACs only. It is important to note that although parenteral nutrition has been validated as a risk factor for PABSI, we could not investigate this point since only one patient was concerned in our nested study. Also, we did not assess the predictive value of certain types of cancers as we did not categorize them more precisely.

No significant difference was found for sex or age between both groups, meaning that these factors are not predictive for PABSI occurrence. This statement is in agreement with available literature (3,14,22), although one report showed that patients aged of more than 55 years old have a higher incidence rate of PABSI (10).

We found that neutropenia is an independent predictive factor for PABSI (p=0.042). Neutropenia results in an immune defect that has been known for a long time to increase infection rates (16). Grade 4 neutropenia (i.e. less than 500 neutrophils/µl) was already defined as a risk factor for CRBSI (3). Here we show that a higher threshold of neutropenia, defined as 1800 neutrophils/µl in our institution, is already significant for PABSI occurrence. When available, overall means of cumulative neutropenia time during time to outcome were calculated but were not statistically different between cases and controls (5.6 days (range: 0-63) in cases vs. 4.8 days (range: 0-53) in controls, p=0.78). Lack of a competent immunity may result in an easier proliferation of pathogens that already colonize PAC lumen or catheter tip. Interestingly, no other source of immunosuppression (i.e. recent use of chemotherapy, radiotherapy or glucocorticoids) showed any statistical difference between groups. Other hematological deficiencies on outcome date (i.e. anemia and thrombocytopenia) were not retained as predictive factors in our analysis.

The population for our comparative analysis comprised 7.7% of diabetic patients which is similar to local incidence of diabetes mellitus (around 5%) (27). Diabetes mellitus (DM) was defined as an independent risk factor for PABSI in multivariate (p=0.044). Current evidence states that hyperglycemia leads to phagocyte dysfunction through various mechanisms (26). It also favors

Candida and other fungal species proliferation. Many common infections, such as skin and soft tissues infections, are more common in diabetic population (28). The role of diabetes in PABSI remains controversial, though, and needs further investigation. Indeed, Yoshida et al. (11) compared patients with PABSI to controls and did not retain DM as a predictive factor (OR adjusted: 1.026; 95% CI: 0.494-2.130; p=0.945). Similarly, Touré et al. (21) recently showed that diabetes did not significantly play a role in BSI in a PAC-carrying population with a DM prevalence of 21.3% (cumulative incidences of PABSI : 12.7% in controls vs. 5.9% in DM1, p=0.70; vs. 19.7% in DM2, p=0.17, respectively).

Interestingly, cases with documented infection on outcome date caused by a different pathogen and in another location than the PAC were more at risk for PABSI than controls (p=0.012). This may show a correlation between these two variables rather than a causative effect. Indeed, the presence of another infection may be a marker of patient's immune system vulnerability and repeated careful examination of PAC insertion site should then be established. However, we cannot conclude about the usefulness to introduce antibiotics that cover usual PABSI pathogens in this situation, as systemic antibiotic prophylaxis does not decrease the incidence of catheter-related BSI (22). Interestingly, this risk factor was also pointed out by statistical analysis in another recent study but was not further discussed (10). In a same idea, we found that cases had a longer mean hospital stay around outcome date than controls (42 days versus 9 days, p<0.001). This variable includes hospitalization time before and after outcome date and may thus correlate with PABSI occurrence in two ways. It indicates a poorer health condition in case group, resulting either in longer hospitalizations and making cases more vulnerable to PABSI or in a longer time needed for restoring after PABSI.

Acute and chronic renal failures are thought to increase susceptibility to infection via uremic syndrome (29). Yoshida et al. showed no significant difference for PABSI due to renal disease but this designation was not further explained. Here we found that renal failure had no impact in PABSI occurrence according to classical p-value threshold, but nevertheless remained close to significance (p=0.059). The role of this variable and its related pathophysiology may be elucidated by specifying uremia levels in further research. This data was not routinely available in our cohort.

Many patients had another catheter or invasive device than the PAC on outcome date (44% in cases vs. 26% in controls). We hypothesized that this intravascular equipment could be an entry for pathogen colonization. Following the PABSI criteria that we established, other CRBSI have been excluded. Nevertheless they could remain a source of blood seeding and colonization of other localizations, such as PAC's catheter tip or chamber. Carrying another invasive device was not considered as a risk factor by multivariate analysis, though (p=0.059).

Most patients had their PAC in use on outcome date (82% in cases vs. 67% in controls). This factor was not retained in our multivariate analysis, although it may remain decisive for PABSI occurrence. As explained above, colonization and spread on PAC material is a slow process and is most certainly due to repeated punctures through its membrane. Therefore, the cumulative number of punctures or utilization-days may be a more relevant factor as demonstrated by Touré et al. (10). Unfortunately, we were not able to reliably determine these variables due to inconsistent information in medical files.

PABSI were subdivided in degrees of diagnosis confidence. We found no statistical difference in the variables presented above between possible (19 patients), probable (16 patients) and definite groups

(4 patients) (data not shown). Nevertheless, this illustrates the difficulty of clearly defining PABSI retrospectively when local PAC infections signs were absent (24) or not documented, and when culture confirmation methods (such as quantitative cultures of catheter or blood or differential time to positivity summarized by Raad et al. (15)) are not done routinely which is the case of most Swiss hospitals.

Our study is hampered by several limitations. The main ones are inherent to its retrospective design. Our data depend on reliability and quality of documentation in archived medical files. In consequence, we cannot exclude missing data or loss of important information. The external validity of our results was compromised as the study was conducted in one single hospital. However, this design may benefit from a better homogeneity of follow-up and retrospective data; moreover, it allows to assess local PAC –related practices by comparing PABSI rates in our institution with that reported in other studies. PABSI low incidence was another limitation of this study. Our nested case-control study only included 78 patients in 2 years of follow-up, which may not have provided enough sensitivity to identify some risk factors. Moreover, comparisons made between cases and controls were considered as representative of the cohort, but would need confirmation by analyzing these factors in the whole cohort. Finally, follow-up time was inconsistent in the cohort, ranging from 16 to 40 months and therefore missing PABSI that occurred after this limit. Nevertheless, we calculated a median time to PABSI of 179 days that was covered by the smallest follow-up duration.

Conclusion

PACs are considered as the safest long-term intravascular devices in terms of BSI rates. Our study demonstrated that local epidemiology and microbiology of PABSI in our institution was similar to previous reports. Risk factors for developing a CRBSI have been little investigated for PACs. Due to differences in carrying duration and system properties of PACs, they may be somewhat different to classical risk factors for invasive devices. Difficulties in defining universal risk factors between studies may be due to heterogeneous studied populations and emphasis the importance of local research. In our institution, we defined four independent predictive factors for PABSI. Neutropenia, diabetes mellitus and renal failure may cause decreased immunity and thus favor bloodstream infections. In consequence, particular attention should be paid to patients with such conditions. Development of another infection than PABSI is a mark of vulnerable patient's state and may require further measures. Before updating any guidelines in our institution, it would be useful either to confirm these results or to test preventive measures in a larger prospective study.

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Remerciements

Je souhaite remercier chaleureusement les personnes ayant contribuée à la réalisation de ce travail de Master:

- ***Prof. Giorgio Zanetti***, mon tuteur, que je remercie énormément pour m'avoir proposé ce travail, tout le temps qu'il m'a accordé, la partie statistique qu'il a réalisée, les corrections apportées à ce travail et surtout ses conseils et son soutien tout au long de ces 2 ans.

- ***Prof. Oscar Marchetti***, qui aura la tâche d'évaluer ce travail et que je remercie d'avance pour le temps qu'il y consacrera.

- ***Dr. Guy Prod'hom***, du laboratoire de microbiologie du CHUV, que je remercie pour notre discussion sur la définition des bactériémies associées aux Port-a-Cath© et pour nous avoir fourni les données sur les prélèvements microbiologiques utilisés dans cette étude.

- ***Mme Françoise Kolodziejczyk***, responsable qualité des systèmes d'informations des sites opératoires, que je remercie pour nous avoir fourni les statistiques opératoires concernant les Port-a-Cath© au CHUV.

- ***Dr Nicolas Ketterer***, du Centre pluridisciplinaire d'oncologie clinique, que je remercie pour notre discussion au début de ce travail sur les aspects pratiques de l'utilisation des Port-a-Cath© au CHUV.

- ***Dr Adlija Rexhaj***, ma future épouse, que je remercie pour son soutien moral et pour le prêt inconditionnel de son ordinateur sans lequel ce travail n'aurait pu être écrit.