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Antibiotic lock technique combined with systemic antimicrobial therapy for management of port-related bloodstream infections in onco-haematological patients without catheter removal

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Abstract

Background : Port-related bloodstream infection (PRBSI) is a common complication associated with long-term use of ports systems. Systemic antimicrobial therapy (ST) and removal of the device is the standard management of PRBSI. However, a conservative management combining ST with antibiotic lock therapy (ALT) without port removal has been suggested as an alternative management option for infections due to gram-positive skin colonizers with low virulence.

Objectives : i) to assess the frequency of management of PRBSI in onco-hematological patients by combining the ALT with ST, without catheter removal and ii) to analyze the efficacy of such an approach.

Methods : Retrospective observational study over a 6-year period between 2005 and 2010, including patients who where diagnosed with PRBSI and who were treated with ST and ALT. PRBSI diagnosis consisted in clinical signs of bacteremia with blood cultures positive for gram-positive skin colonizers. The primary endpoint was failure to cure the PRBSI.

Results : 61 port infections were analysed, of which 23 PRBSI met the inclusion criteria. All the patients were suffering from haematological conditions and 75% were neutropenic at the time of PRBSI diagnosis. *S. epidermidis* was responsible for 91% of PRBSI (21/23). The median duration of ST was 14 days (range 7-35) and the median duration of ALT was 15 days (range 8-41). Failure to cure the PRBSI requiring port removal was observed in 4 patients, but was not associated with severe infectious complications. Kaplan-Meier analysis showed a success rate in port salvage at day 180 (6 months) of 78% (95%CI 59-97%).

Conclusion : The success rate observed in the present study suggests that combining ST and ALT is an effective option to conservatively treat PRBSI caused by pathogens of low virulence such as *S. epidermidis*.

Background

Long-term implantable central venous catheters have been used for over 40 years (1). Totally implantable venous access devices or "ports" are first described in the article of Belin *et al* in 1972 (2,3). Numbers on totally implantable ports inserted each year are not available in the literature. Mermel *et al* reported in 2001 that more than 5 millions central venous catheters are inserted each year in the United States (4), including port systems. One can assume that their number is growing as daily practice suggests, especially in hematological or oncological patients. There was an estimated total number of 2143 ports implanted at CHUV between 2005 and 2010 according to the "CHOP[1]" code 86.07 encoding for this procedures regardless of the indication for port placement (source: Service of archives and medical coding, CHUV). Because of multiple manipulations during the prolonged use of ports, port-related bloodstream infection (PRBSI) is a frequent complication. A systematic review of 14 prospective studies reported a PRBSI rate of 3.6 episodes/100 ports and of 0.1 episodes/1000 port-days (5). The first step of the pathogenesis of PRBSI is characterized by the colonisation of the catheter hub with biofilm-producing microorganism (6). The main microorganisms involved in PRBSIs are Gram positive cocci, responsible for 65.5% of episodes, including Coagulase-negative staphylococci (mainly *S. epidermidis*), *Staphylococcus aureus*, and *Enterococcus* spp (7–9). Gram negative bacilli account for 21% of cases: *Enterobacteriacae* spp., *Acinetobacter* spp., and *Pseudomonas aeruginosa* (7–9). Gram positive bacilli, e.g. *Corynebacterium* spp, (7–9) and yeasts (*Candida* spp.) account for 10% and 3.5% of cases, respectively (7–9). The standard management of PRBSI includes systemic antimicrobial therapy and catheter removal (7). However, in PRBSI due to coagulase-negative streptococci, some Gram-negative bacilli (*E. coli*, *Enterobacter* spp.) and other Gram-positive microorganisms (*Corynebacterium* spp., *Enterococcus* spp. *S. mitis*), the combination of systemic antimicrobial therapy (ST) and intraluminal therapy, so called "antibiotic-lock therapy" (ALT) without catheter removal, has been suggested as a management option (7–9). The first study reporting antibiotic lock therapy for treating catheter-related bacteraemia by Messing B *et al* in 1988 (10) suggested that catheter-related sepsis can be managed without catheter removal with high success rates by using a "lock" consisting in filling the catheter lumen with 2ml of a highly concentrated antibiotic solution. The rationale of this approach was that antibiotic concentrations 100-1000 times greater than the usual systemic concentrations were able to eradicate bacteria in catheter biofilms and that this was made possible by using the lock technique, without systemic toxicity of high dose antimicrobial therapy (4). The success rate, i.e. catheter salvage, reported in this first study on catheter locks was 91%. Since then, clinical studies have reported catheter-

[1] Swiss catalogue of surgical procedures

salvage rates ranging between 75 and more than 80% (4-6). Nevertheless, most studies have analyzed long-term catheters without distinction between tunneled devices (Broviac, Hickmann) and ports. Four studies treating PRBSI specifically were found: Megged *et al* (11), Sanchez-Munoz *et al* (12) and Del Pozo *et al* (13,14) reported success rates from 18 to 89% for the management of port-related bacteremia with systemic antimicrobial treatment associated with antibiotic lock therapy. 3 other studies focused on treatment of catheter-related bacteremia, regardless on the type of device (15–17): a specific subgroup analysis of ports data showed estimated success rates varying from 77% to 94%. Based on the above data, clinical guidelines recommend this type of treatment for long-term catheter-related bloodstream infections. Data on use of this approach for PRBSI management at Centre Hospitalier Universitaire Vaudois (CHUV) are lacking and a systematic, standardized procedure is not available.

The aim of this study was i) to assess the frequency of management of PRBSI in onco-hematological patients by combining the antibiotic-lock technique with systemic antimicrobial therapy, without catheter removal and ii) to analyze the efficacy of such an approach.

Patients, methods and definitions

Study design. This observational retrospective study included patients with PRBSI hospitalized in the Isolation ward of the Infectious Disease Service of the Department of Medicine at CHUV between January 1st, 2005 and December 31st, 2010. All discharge letters over the study period have been screened in order to identify patients with PRBSI. Those who fulfilled the below inclusion criteria were included. The database of the Laboratory of microbiology (Molis) as well as charts for patients who were followed on an outpatient basis by the Hematology service or the Coordinated centre of oncology (CCO) were used as back-up source for additional information. Demographic, clinical, microbiological, treatment and follow-up data were retrospectively collected using standardized report forms and entered into a database (Microsoft Excel 2007).
Institutional Ethics Committee approval for the use of medical information for research purposes was obtained.

Patients. To be eligible for the study, the patients had to fulfill the following criteria: 1) age more than 18 years and hematological malignancy or solid tumor; 2) presence of a totally implantable device of type Port-a-Cath®; 3) PRBSI treated conservatively with systemic antibiotic therapy (ST) and ALT; 4) no planned removal of the port for reasons other than PRBSI within the following 30 days.
Exclusion criteria were those that required immediate port removal for the PRBSI: pocket or subcutaneous infection, complicated catheter-related infection (septic thrombosis, endocarditis,

osteomyelitis, metastatic seeding), severe sepsis or septic shock, infections with *Candida* spp or *S. aureus* or Gram-negatives. However, because additional data on successful management of Gram-negative PRBSIs with ALT were found after submission of the protocol, it was decided to also include *a posteriori* two cases of Gram-negative bacteremia into the study.

Study definitions. *PRBSI* was defined as clinical signs of bacteraemia (fever > 38°C, chills, hypotension) without another clinically obvious source of infection and positive blood cultures for CoNS or other Gram-positive skin colonizers drawn from the port plus/minus peripheral venipuncture. Qualitative blood cultures were drawn simultaneously from the port and from peripheral venipuncture: PRBSI was diagnosed as soon as one of these cultures were positive concomitantly to the clinical features listed above. Because differential time-to-positivity was not systematically used, this could not be used as a criterion for PRBSI in the present study.
Infection type: community-acquired infection included infections occurring within 72 hours after hospitalization and no former hospital stay during the preceding 3 weeks. Hospital-acquired infection was considered when community-acquired infection criteria were not fulfilled.

Treatment. Only patients who received both ST and ALT were considered. ST was divided into empirical and appropriate treatment as follows: i) empirical ST included any of the antimicrobial drugs given before the diagnosis of PRBSI, i.e. reporting of positive blood culture results from the microbiology lab to the physician in charge, regardless of the in vitro antibacterial susceptibility testing and ii) appropriate treatment was adapted to the in vitro antibacterial susceptibility testing.
ALT was performed by using vancomycin or ciprofloxacin and ports were locked after the end of the ST. Vancomycin locks consisted in 2ml of 5mg/ml vancomycin solution mixed with heparin (Liquemine®) 100 IU/ml. Ciprofloxacin locks contained 2ml of 2mg/ml ciprofloxacin solution mixed with heparin 100 IU/ml. Because there is no systematic protocol on the length of the ALT, all lock durations were included into the study. Lock solutions were conserved in a fridge at 4°C for a maximum of 14 days.

Outcome. *Success* was considered when the following criteria were fullfilled: 1) cure of the acute episode of PRBSI, 2) the catheter being still in place 6 months after PRBSI diagnosis (if the port had to be removed between 3 and 6 months after the end of the treatment for another reason than infection (i.e. end of chemotherapy, thrombosis, port extravasation, port obstruction/dysfunction or another reason) and port culture was sterile, the management was considered as a success), 3) no relapse of PRBSI with the same microorganism, based on the bacterial species identification and antibacterial susceptibility testing profile,

Failure was subdivided into three different types: 1) immediate failure, defined as lack of response of the acute episode of PRBSI requiring removal of the port within 7 days after the start of an appropriate antibacterial treatment, e.g. persistence of fever or persistent bacteremia or any other severe infectious complication (pocket or subcutaneous infection, septic thrombosis, endocarditis, osteomyelitis, metastatic seeding; severe sepsis or septic shock), 2) early failure, defined as a relapse of bacteraemia with the same microorganism (see above) within 7 to 30 days after start of appropriate antibacterial treatment, 3) Late failure, defined as relapse of PRBSI with the same microorganism (see above) between 30 days and 6 months. For patients who died within the evaluation period, additional data were collected in order to assess whether there were any criteria for treatment failure.

Statistical analysis. Statistical analyses were performed using Microsoft office Excel 2007 and XLStat 2011 for Excel.

Results

Figure 1 summarizes the characteristics of 61 patients with PRBSI identified according to the systematic screening of the discharge letters. Data on the 66 microorganisms identified in these 61 episodes of PRBSI are shown in *table 1*. *S. epidermidis* was the most common microorganism regardless of the type of PRBSI-management (ST/ALT, ST/port removal, other) and no PRBSI due to *S. aureus* (7% of all PRBSIs) received ALT. 5 polymicrobial infections were identified: 2 in the ST plus ALT group (*S. epidermidis*/*S. mitis* and *S. epidermidis*/*E. coli)*, 2 in the ST plus port removal group (*E. coli/S. aureus* and *E. coli/K. pneumoniae)* and one due to yeasts (*C. albicans/C. parapsilosis*) was treated with systemic antifungal therapy and port removal.

Of the 61 episodes of PRBSI identified during the study period, 26 (43%) were treated with systemic ST and ALT. 23 of these PRBSIs met the inclusion criteria, 2 episodes could not be analysed because of insufficient data and 1 episode was excluded from the study because it eventually did not receive any ALT.

Clinical characteristics. Demographic, clinical, microbiological and treatment data of the 22 patients with the 23 PRBSIs included into the study are shown in *table 2*. The male:female ratio was 2:1 and all patients were suffering from an haematological malignancy. 1 female patient had concomitant acute myeloid leukaemia and breast cancer. 21/23 (87%) patients were undergoing chemotherapy, 10 of which could not be classified into subgroups because of the heterogeneity of the treatments. Neutropenia (<0.5 G/l) was present in 17/23 (74%) of the patients at the time of PRBSI diagnosis. Port location was subclavian right (9/23, 39%) or left(10/23, 43%), 1 patient had

a left femoral vein location and in 3/23 (13%) location information was not available. The most common clinical manifestation of PRBSI was fever (91%, 2 patients had no fever, but positive port blood cultures) and none of the patients who received ALT had any purulent discharge. In 20 PRBSI episodes blood cultures were drawn simultaneously from both the port and peripheral venipuncture, while in 3 episodes blood cultures were only drawn from the port. 88/111 (79%) port blood cultures bottles were positive in 23/23 (100%) PRBSI episodes, while 28/83 (34%) peripheral blood cultures bottles were positive in 8/23 (34%) PRBSI episodes. Among positive port blood cultures, the following distribution of the number of positive bottles was observed: 4/4 positive bottles in 52% (12/23) PRBSI episodes, 3/4 positive bottles in 22% (5/23), 2/4 positive bottles in 4% (1/23), and other proportions of positive bottles in 22% (5/23) (5/8 in 1, 4/8 in 1, 3/3 in 1, 2/2 in 1, and 1/10 in 1). Among concomitant positive peripheral blood cultures, the following distribution of the number of positive bottles was observed: 4/4 in 62% (5/8), 3/4 in 25% (2/8), 2/4 in 25% (1/8). When peripheral blood cultures bottles were 4/4 positive (5/8 episodes), port blood cultures were positive with 4/4 bottles in 3 episodes, 3/4 bottles in 1 and 5/8 bottles in 1. When peripheral blood cultures bottles were 3/4 positive (2/8 episodes), port blood cultures were positive with 2/2 bottles in 1 episode and 4/4 in 1.For the 1 episode with 2/4 positive peripheral blood culture bottles, 4/4 positive port blood culture bottles were observed. Two episodes might have been misdiagnosed and could consist of contamination rather than real PRBSI episodes: the first one had 1/10 positive port blood culture without any positive peripheral blood culture and the second one only had 2/4 positive port blood cultures without any positive peripheral blood culture. Microbiological data of the PRBSIs included into the study are shown in *table 2*. *S. epidermidis* was identified in 21/23 (91%) PRBSI. Gram-negatives were documented in 2 PRBSI : i) a co-infection with *S. epidermidis* and *E. coli,* probably reflecting a translocation due to GI-tract mucositis rather than a PRBSI, which was however managed as a PRBSI with an ALT combining vancomycin and ciprofloxacin, ii) an *E. cloacae* PRBSI, which occurred as a late complication of a GI-tract mucositis-associated bacteremia and was managed with a ciprofloxacin ALT. Despite being due to gram-negatives, as these PRBSI were both treated with ST and ALT, they were *post-hoc* included into the study. 4/24 PRBSIs were community-acquired infections. Detailed individual characteristics on microbiology, treatment and outcome of the 23 episodes of PRBSI included into the study are presented in *table 3*. Note that PRBSI 8 and 9 occurred in the same patient at an interval of more than 12 months and were analysed separately, as the causative pathogen presented a different antibacterial susceptibility testing profile.

Systemic therapy. Three patients did not receive any empirical therapy and among the remaining 20 who did, 4 (20%) empirical therapies were not appropriate. The median duration of appropriate ST was 14 days (range 7 – 14 days). 20/23 PRBSIs (87%) received vancomycin as a

component of the ST. Median duration of vancomycin therapy was 7 days (range 1 – 19 days). Thirty-seven vancomycin through blood concentrations (VTBC) measurements were performed in 16 patients. The overall median VTBC was 14.35 mg/l (range 4.30 – 36.40 mg/l) (n=16). Median VTBC higher than 10mg/l was reached in 12/16 patients (75%) and median VTBC higher than 15mg/l in 7/16 patients (44%). Median time from PRBSI diagnosis to achievement of VTBC higher than 10mg/l was 2 days (range -13 – 10 days) (n=14). Median time to VTBC higher than 15 mg/l was 3 days (range -13 – 14 days) (n=9). A great variability was observed among the antimicrobial drugs used for the management of PRBSIs (see table 3): median 3, ranging from 1 to 7.

ALT therapy. Vancomycin locks were used in 21/23 PRBSI (91%). The remaining 2 locks consisted in ciprofloxacin (n=1) that was used to treat successfully a PRBSI due to *E. cloacae* and in vancomycin plus ciprofloxacin (n=1) that was used to treat a polymocrobial PRBSI due to *S. epidermidis* and *E. coli.* Concerning this last patient, he died 7 days after the initiation of ALT, while no criteria for PRBSI treatment failure were found. A great variability of the lock duration was observed, ranging from 8 to 41 days. The exact duration time was lacking for 6/23 locks (26%) and the exact indwelling time of the lock solution within the catheter was not available. The lock solution was exchanged daily as long as the patient was hospitalized and weekly as soon as the patient was discharged (outpatient management). 10/23 locks (43%) lasted 2 weeks or more (range 14 – 41 days) and only 1 failure occurred (22 days of ALT). 7/23 locks (30%) lasted less than 2 weeks (range 8 – 12). Among those seven locks, 2 (29%, 8 and 12 days) were stopped because of early treatment failure, 4 were successful (57%, range: 8 – 12 days), and 1 was lost to follow-up.

Outcome. On day 180 (6 months), treatment was successful in 12/23 PRBSI and none of the patients had had their port removed for another reason than infection. Three patients died within the evaluation period without any criteria for treatment failure: the PRBSI was not the cause of death (all patients died because of cancer progression). 4 patients were lost to follow-up because they were transferred to another centre. Those 7 patients were considered as dropouts for the time-event analysis. Failure occurred in 4/23 of the PRBSI treated with ST and ALT: 2 early failures and 2 late failures (see *table 3*). Regarding early failures, patient 14 presented a new PRBSI on day 12 after the initial PRBSI diagnosis. Although both PRBSIs were due to *S. epidermidis,* their antimicrobial susceptibility testing profiles were different which suggested a new infection rather than a relapse. The patient had been under a vancomycin lock for 8 days at the time failure occurred. The port was removed on day 12. Patient 19 presented a relapse on day 12 after PRBSI diagnosis and had already been receiving a vancomycin lock for 12 days. The port was removed on the same day. Regarding late failures, patient 2 and 15 presented a relapse on day 40 and 46, respectively. Their ports were removed 3 days after relapse diagnosis. Only one patient who

presented treatment failure was neutropenic at the time of diagnosis and in none of the failures severe PRBSI-associated complications occurred. A Kaplan-Meier analysis was performed in order to determine the cumulative 6-month success rate. When all the 23 episodes were analysed, a cumulative 6-month success rate of 78% (95% CI, 59 – 97%) was observed. Analysing only the PRBSI episodes that could be evaluated until the end of the 6-month study period (n=16), the cumulative success rate was 75% (95% CI, 53 – 96%). *Figure 2* shows the cumulative success rate for episodes that could be evaluated until the end of the study period. Of note, patient 8 presented a late relapse on day 205 after PRBSI diagnosis.

Discussion

This study confirms the data reported in the literature on PRBSI management with ST and ALT, with an estimated 6-month cumulative success rate of around 75%. Although the number of patients was low, many of the above mentioned studies had similar samples sizes, ranging from 14 to 44 PRBSI (11–17). These data suggest that actual conservative management of selected cases of PRBSI in our centre is effective. Another point of interest is the fact that follow-up in this study was conducted over a period of 6 months (180 days) after PRBSI diagnosis showing that management with ALT can be beneficial in a long-term perspective. Many of the studies that yielded success rates higher than 80% assessed outcome 30 days after the end of the treatment (13,15,17) and 2 studies with longer follow-up periods of 180 and 90 days showed lower success rates of 77% (16) and 18% (11), respectively. This last result was observed in onco-haematological children: 6/17 of them were neutropenic. Although a comparison between this paediatric population and that analysed in the present study cannot be made, neutropenia don't seem to have played a role in our study showing a 75% success rate despite 75% of patients being neutropenic at time of PRBSI diagnosis.

As far as PRBSI diagnosis is concerned, there is still some discussion about the most appropriate diagnostic criteria. Although clinical signs of bloodstream infection are constantly used in the literature, the best method to diagnose PRBSIs remains controversial. A meta-analysis of 51 studies on the *best methods for diagnosing intravascular device-related bloodstream infection* conducted by Safdar *et al* came to the conclusion that "for long-term catheters (including ports) paired quantitative blood cultures are the most accurate test for diagnosing intravascular device-related bloodstream infection without device removal" (18). They also mention that "clinical findings are unreliable because of their poor sensitivity and specificity". For the present study, any positive blood culture drawn from the port or peripheral venipuncture and growing a pathogen consistent with PRBSI (i.e. Gram positive skin colonizer) combined with consistent clinical

manifestations of infection and the absence of an alternative source of infection were used for defining PRBSI. Some of the studied PRBSIs might thus have represented a port colonisation or blood culture contamination. However, as the studied population was at high risk for infections (neutropenic patients undergoing chemotherapy), the lower diagnostic threshold for PRBSI used by the physicians in charge was an acceptable pragmatic approach.

Rijnders *et al* published in 2004 the first randomized, placebo-controlled trial on ALT for catheter related bacteraemia with catheter salvage on day 180 in 77% for the ST and ALT arm (n=23) versus only 43% for the ST and placebo arm (n=16) (16). Interestingly, the 2 Kaplan-Meier time to treatment failure analysis curves overlap during the first weeks, with most failures in the placebo arm occurring after 2 months. This observation does suggest the efficacy of the management applied in the present study, starting with ST followed by ALT. However, the timing of start ALT and the dwell time needed for "sterilizing" the port remain matter of controversy. Although data on dwell time of ALT were not available for the present study, median duration of ALT was 14 days and in the majority of cases ALT was performed on a weekly outpatient basis. Given the observed success rate, this seems to support vancomycin activity during at least 2 weeks in port lumens (19). Another interesting finding is that patients who received only one week of ALT had favourable outcomes, suggesting that shorter ALT durations may be effective. One study tested the efficacy of a 3-day ALT and reported a success rate of 85.7% (12).

The main limitations of this observational study are the selection bias due to the retrospective design and the low number of eligible patients. Only patients whose discharge report mentioned ST and ALT were selected. As ST always preceded ALT in the present approach, patients in whom port salvage with ALT following ST might have been the initial "intention-to-treat" option but who failed to respond to ST and required early port removal were not identified. This might have led to an overestimation of the success rate. Possible port blood cultures contaminations treated as PRBSI in 2 cases might have been another source of overestimation of the success rate, which illustrates the difficulty of diagnosis and management of PRBSI in clinical practice. The definition of PRBSI used by the physicians in charge for applying the ALT was less strict than in previous studies and in the current guidelines, but does reflect the real-life approach. Concerning the patients lost to follow-up, they were all managed by external centres/physicians and outcome data were not available.

In conclusion, ST followed by ALT without port removal is an effective approach for management of PRBSI due to Gram positive skin microorganisms in onco-haematological patients. Although prospective double-blind randomized trials are needed to prove these results, there has been a

growing evidence in the last few years that the conservative management of PRBSI is an efficient option for of pathogens of low virulence. If port removal remains the recommended standard for more virulent pathogens such as *S. aureus*, *Candida* spp., *P. aeruginosa* and other Gram negatives, the development of new lock solutions such as ethanol or taurolidine may offer new effective options (20).

Conflict of interest statement. None to declare.

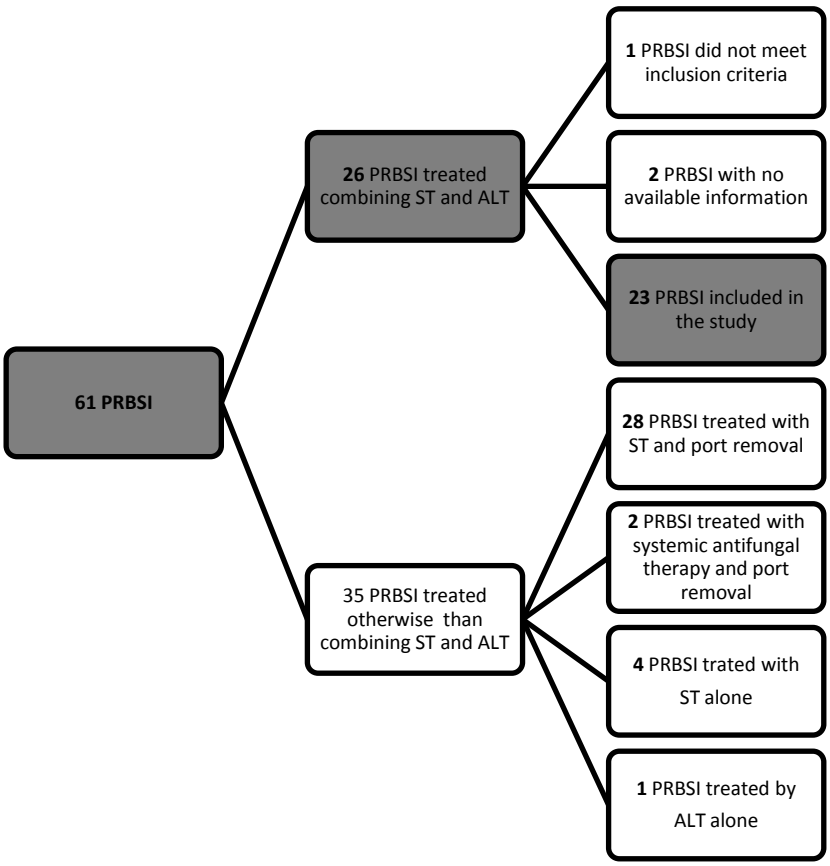

Figure 1. Algorithm of patients selection according to systematic screening of the discharge reports of the Isolation Ward of the Infectious Diseases Service at the Department of Medicine (CHUV), between January 1, 2005 and December 31, 2010.

Table 1. Microbiological data of the 61 episodes of PRBSI that occurred in the Isolation Ward of the Infectious Disease Service at the Department of Medicine (CHUV) over a 6-year period.

General microbiological caracteritics of the 61 PRBSI	
Number of miccroorganisms involved	66
Polymicrobial infection	5
Overall microorganism repartition(%)	
Gram-positive bacteria	71%
S. epidermidis	62%
S. aureus	7%
E. gallinarum	3%
S. mitis	2%
S. haemolyticus	2%
Gram-negative bacteria	17%
E. coli	10%
E. cloacae	3%
K. pneumoniae	2%
C. koseri	2%
Stenotrophomonas malto	2%
Other	11%
C. albicans	3%
S. agalactiae	2%
C. parapsilosis	2%
unknown	5%
sterile cultures	2%
Microorganism repartition according to PRBSI management type (%)	
ST and ALT (n=26)	
Gram-positive bacteria	89%
S. epidermidis	79%
E. gallinarum	7%
S. mitis	4%
Gram-negative bacteria	7%
E. cloacae	4%
E. coli	4%
unknown	4%
ST and port removal (n=28)	
Gram-positive bacteria	63%
S. epidermidis	43%
S. aureus	13%
S.agalactiae	3%
S. haemolyticus	3%
Gram-negative bacteria	27%
E.coli	17%
S. maltophila	3%
C. Koseri	3%
K. pneumoniae	3%
unknown	7%
Other (ST alone, AFT and port removal, ALT alone) (n=7)	
Gram-positive bacteria	50%
S. epidermidis	50%
Yeasts	38%
C. albicans	25%
C. parapsilosis	13%
sterile culture	13%

ST= Systemic antimicrobial Therapy; **AFT**= systemic AntiFungal Therapy; **ALT**= Antibiotic Lock Therapy.

Table 2. Demographic and clinical characteristics of the 22 patients included in the study with 23 episodes of PRBSI.

Patients	22	
Age (median) (range)	60	(23 - 78)
Gender		
Male (%)	68%	
Female (%)	32%	
Underlying disease		
Hematological malignancies	22/22	
Acute myeloid leukemia	6/22	
Myelodyspasic syndrome	1/22	
Multiple myeloma	6/22	
Non-Hodgkin lymphoma	6/22	
Hodgking lymphoma	3/22	
Solid tumor	1/22	
Episodes of hospitalization	23	
Type of chemotherapy		
Consolidation AL	1/23	
Autologous-HSCT	8/23	
Allogenic-HSCT	2/23	
Other	10/23	
None	2/23	
Neutropenia (%)	74%	
Median Duration (days)	7	
Range (days)	2 - 79	
Port location (%)		
Subclavian right	39%	
Subclavian left	43%	
Other	4%	
Unknown	13%	
Time elapsed from port placement to PRBSI diagnosis (n=15)		
Median (days)	164	
Range (days)	3 - 1104	
Clinical Presentation		
Systemic manifestations		
Fever	91%	
Median duration (days)	3	
Range (days)	1 - 13	
Chills	30%	
Sepsis	30%	
Local signs of infection		
Redness	17%	
Calor	4%	
Oedema	13%	
Pain	22%	
Purulent discharge	0%	

Table 2 (continued)

Bacteremia characteristics according to the number of episodes of PRBSI		
Length of bacteremia (days) (n=21)		
(median) (range)	1	(1 - 6)
Blood cultures		
PAC blood cultures		
Positive PAC blood cultures/total episodes of PRBSI (%)	23/23	100%
Total No of positive bottles/total No of bottles (%)	88/111	79%
Peripheral blood cultures		
Positive peripheral blood cultures/total episodes of PRBSI (%)	8/23	34%
Total No of positive bottles/total No of bottles (%)	28/83	34%
Total No of positive blood culture bottles (PAC + peripheral) /total No of bottles	116/194	60%
PRBSI diagnosis		
Median time elapsed from blood sample to PRBSI diagnosis (days) (range)	1	(1 - 4)
Median time elapsed from blood sample to appropriate antimicrobial treatment (days)(range)	0	(-1 - 3)
Microorganisms		
Gram-positive organisms		
S. epidermidis	21/23	
S. mitis	1/23	
E. gallinarum	1/23	
Gram-negative organisms		
E. cloacae	1/23	
E. coli	1/23	
Polymicrobial infections		
S. epidermidis / S. mitis	1/23	
S. epidermidis / E.coli	1/23	
Antimicrobial treatment		
Appropriate ST duration in days (median) (range)	14	(7 - 35)
ALT duration in days (n=16) (median) (range)	15	(8 - 41)
Median time elapsed from PRBSI diagnosis to appropriate antimicrobial treatment (days)(range)	-1	(-3 -1)
Median time elapsed from PRBSI diagnosis to ALT (days)(range)	6	(-1 - 21)
Outcome		
Success	12/23	
Failure	4/23	
Immediate	0/23	
Early	2/23	
Late	2/23	
Patients dead within evaluation period without known failure criteria	3/23	
Patients lost to follow-up	4/23	

AL= Acute Leukemia; **HSCT**= Hematopoietic Stem Cell Transplantation; **ST**= Systemic Therapy; **ALT**= Antibiotic Lock Therapy.

Table 3. Individual microbiological, treatment and outcome characteristics of the 23 episodes of PRBSI included in the study.

Patient	Age	Gender	Microorganism	Type of infection	PBC	PVC	ST												ALT		Outcome
							Empirical	Route	Length[a] (days)	Pathogen susceptible	Adjusted	Route	Lentgth (days)	Total (days)	Vancomycin use	vancomycin therapy duration (days)	Number of RTBC	RTBC (median)	RTBC (range)	Drug	Length (days)	
1	23	M	*S.epidermidis*	HA	+	+					vancomycin	i.v.	S.D.	14	yes	14	3	14.10	4.30 - 17.10	vancomycin	14	**success**
											vancomycin	i.v.	S.D.									
2	56	M	*S.epidermidis*	HA	+	+	co-amoxicilline	i.v.	1	yes	co-amoxicilline	i.v.	9	14	yes	1	0	none		vancomycin	unknown	**late failure**
							vancomycin	i.v.	2	yes	co-amoxicilline	p.o.	5									
3	60	M	*S.epidermidis*	HA	+	+	cefepime	i.v.	1	yes	cefepime	i.v.	6	14	yes	14	3	20.75	13.00 - 32.00	vancomycin	15	**lost to follow-up**
											vancomycin	i.v.	14									
4	30	M	*S.epidermidis*	HA	+	-	cefepime	i.v.	3	yes	vancomycin	i.v.	4	35	yes	4	2	9.65	4.50 - 14.80	vancomycin	unknown	**lost to follow-up**
											cefepime	i.v.	3									
											teicoplanin	i.v.	12									
											clindamycin	p.o.	16									
											rifampicine	p.o.	17									
5	54	F	*S.epidermidis*	HA	+	-	cefepime	i.v.	5	no	meropenem	i.v.	10	11	yes	4	1	27.90		vancomycin	8	**success**
							vancomycin	i.v.	4	yes	cubicine	i.v.	11									
											levofloxacin	p.o.	3									
6	47	F	*S.epidermidis*	HA	+	-	vancomycin	i.v.	16	yes	pip/tazo	i.v.	1	8	yes	4	2	13.80	11.70 - 15.90	vancomycin	8	**success**
							pip/tazo	i.v.	12	no	daptomycine	i.v.	7									
							daptomycine	i.v.	9	yes	ciprofloxacine	p.o.	6									
7	65	F	*S.epidermidis*	CA	+	-	imipenem	i.v.	4	yes	vancomycin	i.v.	7	7	yes	7	0	none		vancomycin	16	**1**
8	32	M	*S.epidermidis*	CA	+	+	imipenem	i.v.	3	no	teicoplanin	i.v.	14	14	no					vancomycin	unknown	**success**
9	31	M	*S.epidermidis*	HA	+	none	vofloxacinacine	p.o.	2	no	vancomycin	i.v.	4	15	yes	4	2	24.75	19.80 - 29.70	vancomycin	unknown	**success**
											teicoplanin	i.v.	12									
10	68	M	*S.epidermidis*	HA	+	-					co-amoxicilline	i.v.	13	13	no					vancomycin	29	**success**
11	66	F	*Enterobacter cloacae*	HA	+	none	imip/cilas	i.v.	2	yes	cefepime	i.v.	3	15	no					ciprofloxacine	12	**success**
											imip/cilas	i.v.	9									
											ciprofloxacine	p.o.	4									
12	78	M	*S.epidermidis*	CA	+	+					vancomycin	i.v.	4	21	yes	4	1	20.80		vancomycin	unknown	**lost to follow-up**
											levofloxacin	i.v.	10									
											levofloxacin	p.o.	7									
13	59	M	*S.epidermidis*	HA	+	+	imip/cilas	i.v.	2	yes	imip/cilas	i.v.	5	24	yes	1 (single dose)	3	30.20	29.40 - 36.40	vancomycin	37	**success**
											vancomycin	i.v.	6									
											flucloxacilline	i.v.	1									
											cefepime	i.v.	3									
											ceftriaxone	i.v.	2									
											linezolide	p.o.	10									
											rifampicine	p.o.	10									

Table 3 (continued)

14	26	M	*S.epidermidis*	HA	+	+	cefepime i.v.	3	yes	cefepime i.v.	6	14	yes	4	2	14.25	8.80 - 19.70	vancomycin	8	**early failure**
							vancomycin i.v.	2	yes	vancomycin i.v.	2									
										levofloxacin p.o.	5									
15	64	M	*S.epidermidis*	HA	+	-	cefepime i.v.	2	yes	cefepime i.v.	3	10	yes	8	2	9.95	9.40 - 10.50	vancomycin	22	**late failure**
										vancomycin i.v.	10									
16	64	F	*Enterococcus gallinarum*	HA	+	-	vancomycin i.v.	2	yes	vancomycin i.v.	14	14	yes	16	0	none		vancomycin	41	**success**
17	29	M	*S.epidermidis + S.mitis*	HA	+	-	cefepime i.v.	2	no	cefepime i.v.	2	8	yes	5	2	8.25	6.60 - 9.90	vancomycin	9	**success**
										vancomycin i.v.	7									
										imip/cilas i.v.	5									
										linezolide p.o.	1									
18	63	M	*S.epidermidis*	HA	+	-	vancomycin i.v.	1	yes	vancomycin i.v.	18	18	yes	19	2	14.45	12.70 - 16.20	vancomycin	24	**success**
										rifampicine p.o.	18									
19	70	F	*S.epidermidis*	HA	+	-	cefepime i.v.	3	yes	cefepime i.v.	4	12	yes	4	1	13.00		vancomycin	12	**early failure**
										vancomycin i.v.	4									
										ciproflox p.o.	9									
										rifampicine p.o.	8									
20	59	M	*S.epidermidis*	HA	+	-	cefepime i.v.	1	no	vancomycin i.v.	7	7	yes	7	1	9.30		vancomycin	8	**lost to follow-up**
										cefepime i.v.	5									
21	57	M	*S.epidermidis*	HA	+	-	cefepime i.v.	2	yes	cefepime i.v.	4	20	yes	4	0	none		vancomycin	15	**success**
										imip/cilas i.v.	8									
										vancomycin i.v.	6									
										levofloxacin p.o.	8									
22	60	M	*S.epidermidis*	HA	+	none	imip/cilas i.v.	1	no	imip/cilas i.v.	3	15	yes	11	7	16.30	14.60 - 35.80	vancomycin	24	**1**
							clarythromycin i.v.	1	no	clarythromycin i.v.	3									
										vancomycin i.v.	11									
										levofloxacin p.o.	11									
24	76	F	*S. epidermidis + E.coli*	CA	+	+	cefepime i.v.	2	yes	cefepime i.v.	8	17	yes	17	3	18.40	13.00 - 20.80	vancomycin	unknown	**1**
										vancomycin i.v.	17							ciprofloxacine	unknown	
										ceftriaxone i.v.	6									

[a]= length from the start of the empirical systemic antimicrobial therapy to the diagnosis of PRBSI.

PBC= Port Blood Culture**; PVC=**Peripheral venipuncture blood culture**; ST=** Systemic Therapy; **ALT=** Antibiotic Lock Therapy; **HA**= hospital-acquired infection; **CA**= community-acquired infection; **pip/tazo**= piperacillin-tazobactam; **imip/cilas**= imipenem-cilastatine; **RTBC**= residual through blood concentration. **1=** patient dead within the evaluation period (note that no criteria of treatment failure was found in these patients).

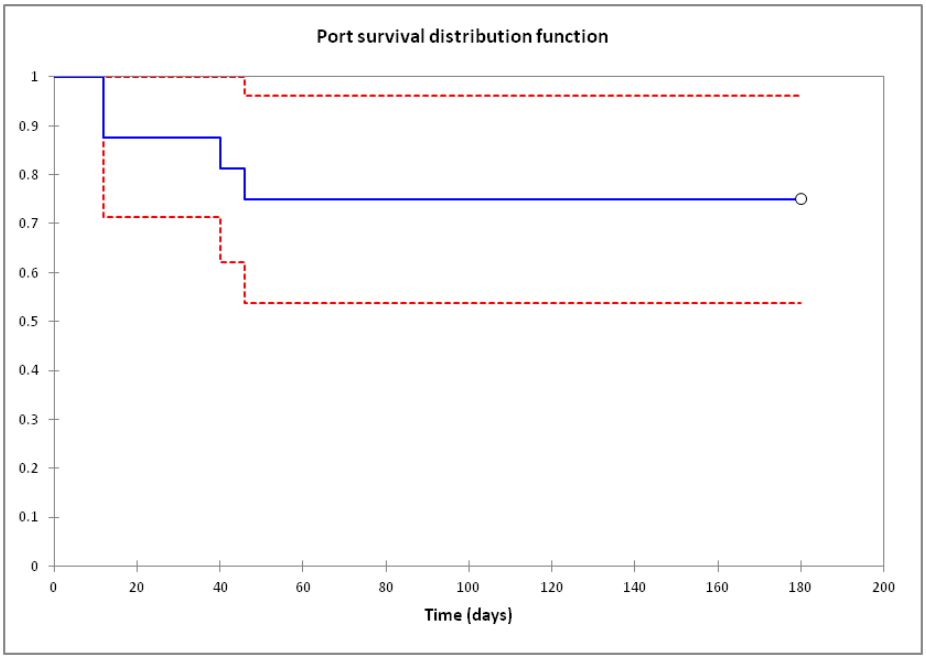

Figure 2. Kaplan-Meier analysis of successful port salvage after ST and ALT during the 180-day study period (n=16). Dotted lines represent the 95% confidence intervals.

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