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Port-A-Cath infections in children with cancer

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Abstract

Implanted subcutaneous (s.c.) central venous port accesses including Port-A-Cath (PAC) facilitate the administration of chemotherapy or blood products and are frequently used in children with cancer. The incidence of PAC-related infections was determined in 155 consecutive paediatric cancer patients with PAC followed for a total of 134,773 days (median, 738; range, 25–2080). Overall, 48 bloodstream infections occurred in 26 patients. 12 (25%) of these infections and 3 local infections at the insertion site were treatment-resistant and demanded removal of the PAC. Coagulase-negative staphylococci were involved in 12 of these 15 episodes. The rate of clearly PAC-related infections in this so far largest reported series was 0.11 episodes per 1000 PAC days, one of the lowest in the literature. Although catheter-related infections demanded PAC removal in 8% of our patients, the long periods PAC were in use and their benefits argue for continued PAC use in the paediatric cancer population.

Keywords: Central venous access device; Central venous catheter complication; Infection; Cancer; Chemotherapy

1. Introduction

Long-term central venous access devices facilitate the administration of cytotoxic drugs, antibiotics, blood products, fluids, parenteral nutrition and the collection of blood samples in children with cancer. Tunnelled, cuffed, silastic central venous catheters, first described by Broviac and colleagues [1] and subsequently modified by Hickman and colleagues [2] provide trouble-free function for most patients. However, catheter-related bloodstream infections occur at a rate of 1.0–2.9 episodes per 1000 catheter-days [3–6]. Since an obvious route of bacterial invasion in patients with Hickman catheters is the open wound maintained by the inserted catheter, efforts at reducing infection have focused on eliminating this wound. One such effort has been the development of totally implantable access ports including the Port-A-Cath (PAC; Deltec, USA) [7]. In addition, such a port is preferable to an external device, since it causes fewer limitations to the child's lifestyle.

Several reports have suggested that PAC-related infections in paediatric cancer patients are so rarely encountered that their frequency and severity are acceptable, and strongly encourage their use [4,8–11]. However, other authors have considered PAC-related infections to be relatively frequent [12,13]. Therefore, the purpose of this study was to analyse the infectious complications arising from placement and management of PAC in a large consecutive series of unselected paediatric cancer patients, treated at a single institution.

2. Patients and methods

2.1. Selection of patients and follow-up

We retrospectively reviewed all 155 paediatric cancer patients, in whom a PAC was surgically placed in the

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period between January 1, 1997 and December 31, 2001 at the University Children's Hospital of Zurich, Switzerland. These patients were followed until December 31, 2002. Within the study period, 84% of all paediatric cancer patients treated with chemotherapy at the University Children's Hospital of Zurich received a PAC.

2.2. Devices and their use

The type of implanted access port was a single lumen Port-A-Cath (Pharmacia AG, Dübendorf, Switzerland) in 142 patients and a BABYPORT (B. Braun Medical, France) in 13 patients with body weight below 10 kg. All PAC implantations were performed under general anaesthesia by experienced paediatric surgeons. The PAC were inserted via the subclavian vein using an infraclavicular approach and fixed to the pectoral muscles. No perioperative antimicrobial prophylaxis was administered. No serious perioperative complications were observed. PAC were accessed or flushed once per two months as a minimum. Trained doctors accessed the devices with isopropyl alcohol skin preparation and sterile, minimal-touch technique. All infusions, including medications, parenteral nutrition fluids and blood product transfusions were administered through the PAC. The majority of diagnostic venous blood samples, including blood cultures, were obtained from the PAC. Three ml heparinised (100 E/ml) saline was used on all occasions to flush the PAC before the needle was removed. The needle was changed every 7 days during periods of prolonged, continuous venous access. During high-dose chemotherapy and bone marrow transplantation, multilumen tunnelled Hickman or Cook catheters were implanted and the PAC not used because of the anticipated need of more than one central line.

2.3. Definitions

Signs of PAC contamination were defined as multiple episodes of bloodstream infection with detection of the same microorganism or repeated detection of the same microorganism for $\geqslant 3$ days despite appropriate antibiotic therapy according to susceptibility testing. PAC-related local infections were defined as infections of the tunnel or the subcutaneous PAC pocket as demonstrated clinically and by ultrasound imaging [14]. Isolated local skin infections over the port were not included in this definition. All of these episodes were treated successfully by ceasing use of the device and application of local wound care. Absolute infection-related indications for PAC removal [15] included PAC tunnel or pocket infection, persistence of fever and positive blood cultures obtained later than 48 h after the initiation of appropriate antimicrobial therapy, and septic emboli or thrombosis of a large vein. Relative indications included recurrent infections with the same bacterial species, and fungal infection without fungaemia or sepsis [12,16].

2.4. Processing of explanted catheters

Surgical removal of PAC was done under strictly sterile conditions in the operating theatre. Routinely, the whole PAC was placed in a sterile container, immediately transported to the infectious diseases laboratory, and processed in a laminar flow-hood. Sterile saline was flushed via a needle inserted into the PAC through the reservoir and the catheter lumen. The tip segment of the catheter was cut and rolled across a blood agar plate [17]. Cultures growing >5 microbial colonies were considered to be potentially associated with catheter-related infection [18]. Flushed saline, catheter tip and PAC reservoir were each separately placed in fluid culture media.

3. Results

3.1. Demographics of patients

During the 5-year study period, 155 paediatric cancer patients undergoing chemotherapy with PAC were recruited. The median age at cancer diagnosis was 4.9 years (range, 0.0–16.8 years). About 96 (62%) patients were male and 59 (38%) were female. Acute lymphoblastic leukaemia (38.7%), and central nervous system tumours (14.2%) were the most common cancer entities, followed by soft tissue sarcomas (7.7%), Wilms' tumour (7.7%), acute myelogenous leukaemia (7.7%), non-Hodgkin's lymphoma (7.0%), osteosarcoma (3.9%), neuroblastoma (3.9%), Ewing's sarcoma (2.6%), hepatoblastoma (1.9%), Hodgkin's disease (1.3%), histiocytoses (1.3%), hepatocellular carcinoma (0.7%), retinoblastoma (0.7%), and germ cell tumour (0.7%). Central venous access ports were implanted within 0–21 days after cancer diagnosis. Median and total observation time for the implanted PACs were 738 days (range, 25–2080) and 134,773 days, respectively. Median and total time for intensive chemotherapy were 217 days (range, 60–612) and 39,467 days, respectively.

3.2. Bloodstream infections

A total of 48 episodes of bloodstream infections occurred in 26 (17%) patients. Twelve patients presented with more than one episode. This resulted in a rate of 0.36 bloodstream infections per 1000 PAC-days. Coagulase-negative staphylococci (54%), followed by *Escherichia coli* (13%) and streptococci (10%) were the most frequently isolated organisms (Table 1).

The risk for bloodstream infection was higher in patients with leukaemia ($n = 72$; 36 blood stream infections) when compared with the patients with solid

Table 1
Microorganisms isolated from 48 episodes of bloodstream infection, including 12 episodes of PAC-related systemic infections, and three episodes of PAC-related local infections in 155 paediatric cancer patients

Organisms	No. of bloodstream infections ($n = 48$)	No. of PAC-related bloodstream infections ($n = 12$)	No. of PAC-related local infections ($n = 3$)
Gram-positive			
Coagulase-negative staphylococci	26	11	1
Staphylococcus aureus	3		1
Enterococcus faecalis	3		
Streptococcus pneumoniae	1		
Streptococcus spp.	1		
Bacillus spp.	1		1
Gram-negative			
Pseudomonas aeruginosa	2		
Stenotrophomonas maltophilia	1	1	
Escherichia coli	6		
Proteus mirabilis	1		
Klebsiella pneumoniae	1		
Anaerobic organisms	1		
Fungi			
Candida albicans	1		

PAC, Port-A-Cath.

tumours ($n = 83$; 12 bloodstream infections; two-sample test of proportion, $P = 0.0026$). Patients with episodes of bloodstream infections were younger at cancer diagnosis ($n = 26$; mean age 3.8 years, range 0.1–13.0 years) when compared with patients without bloodstream infections ($n = 129$; mean age 6.2 years, range 0.0–16.8 years; two-sample t-test, $P = 0.008$). Since age and diagnosis are not independent variables in paediatric oncology, we performed a subgroup analysis for patients with acute lymphoblastic leukaemia (ALL), the largest subgroup ($n = 60$) of our study cohort in terms of clinical diagnosis. Patients with ALL and with episodes of bloodstream infections were younger ($n = 10$; mean age 4.2 years, range 0.6–13.0 years) when compared with the patients with ALL without bloodstream infections ($n = 50$; mean age 6.4, range 0.6–16.8 years). However, the difference did not reach statistical significance (two-sample t-test, $P = 0.13$).

3.3. PAC-related infections

Overall, 12 (25%) of the 48 bloodstream infections were regarded as clearly catheter-related: 6 episodes due to repeated detection of the same microbial species for $\geqslant 3$ days despite adequate antibiotic therapy, and the other 6 episodes due to multiple episodes of systemic clinical infection with detection of the same microbial species. In these 12 episodes, the PACs were removed as were 3 PACs with subcutaneous abscess of the PAC pocket as detected clinically and by ultrasound imaging (Table 2). The calculated rate of clearly catheter-related infections was 0.11 episodes per 1000 PAC days. Infections that required removal of the PAC occurred at a median of 122 days (range, 25–437) after PAC implantation. All three local infections occurred within 36 days after PAC implantation. In all 15 episodes, PAC removal became necessary during intensive cytotoxic chemotherapy. No PAC had to be removed during maintenance chemotherapy or after the end of chemotherapy. Patients whose PAC had to be removed due to infection were younger at cancer diagnosis ($n = 13$; mean age 3.3 years, range 0.1–13.0 years) when compared with patients without infection-related PAC removal ($n = 142$; mean age 6.1 years, range 0.0–16.8 years; two-sample t-test, $P = 0.029$).

Bloodstream infections that required PAC removal were caused by coagulase-negative staphylococci in 11 (92%) of 12 cases and in one case by *Stenotrophomonas maltophilia* (Table 1). Coagulase-negative staphylococci were significantly more frequently isolated from bloodstream infections requiring PAC removal than from other bloodstream infections (11/12 vs. 15/36; Fisher's exact test, $P = 0.0024$). PAC-related local infections requiring PAC removal were caused by coagulase-negative staphylococci ($n = 1$), *Staphylococcus aureus* ($n = 1$), and *Bacillus spp.* ($n = 1$).

Contamination of the PAC was directly confirmed in all 3 PAC-related local infections and in 7 of 12 PAC-related systemic infections (Table 2). In these, organisms isolated from the explanted PAC were of the same species as those isolated from blood cultures drawn through the PAC. In one patient (No. 2), coagulase-negative sta-

Table 2
Clinical and laboratory characteristics of 13 patients whose PAC were removed because of treatment-resistant systemic or local infection

Patient No.	Age at cancer diagnosis (years)	Cancer	Type of PAC infection	Days between implantation and removal of PAC	Indication for PAC removal	Isolated organism from explanted PAC or wound
1a	0.1	AML (M7)	Local	25	Cellulitis with subcutaneous abscess of PAC pocket	Coagulase-negative staphylococcus
1b	0.1	AML (M7)	Systemic	437	Two episodes of systemic clinical infection within 3 weeks; PAC blood cultures each time positive for coagulase-negative staphylococci	Coagulase-negative staphylococcus
1c	0.1	AML (M7)	Systemic	74	Two episodes of systemic clinical infections within 3 weeks; PAC blood cultures each time positive for coagulase-negative staphylococci	–
2	0.8	AML (M7)	Systemic	276	One episode of systemic clinical infection; PAC blood cultures 4× positive for *Stenotrophomonas maltophilia* within 3 days	*Stenotrophomonas maltophilia* + coagulase-negative staphylococci
3	1.2	AML (M5)	Systemic	52	One episode of systemic clinical infection; PAC blood cultures 2× positive for coagulase-negative staphylococci within 7 days	Coagulase-negative staphylococci
4	1.6	ALL (T-cell)	Systemic	133	One episode of systemic clinical infection; PAC blood cultures 3× positive for coagulase-negative staphylococci within 7 days	Coagulase-negative staphylococci
5	13.0	ALL (pre-B)	Systemic	193	Two episodes of systemic clinical infection within 2 weeks; PAC blood cultures each time positive for coagulase-negative staphylococci	Coagulase-negative staphylococci
6	2.5	ALL (common)	Local	30	Cellulitis with subcutaneous abscess of PAC pocket	Bacillus spp.
7	7.9	ALL (common)	Local	36	Cellulitis with subcutaneous abscess of PAC pocket	*Staphylococcus aureus*
8	3.7	NHL	Systemic	95	One episode of systemic clinical infection; PAC blood cultures 2× positive for coagulase-negative staphylococci within 3 days	–
9	1.4	Medullo-blastoma	Systemic	122	Two episodes of systemic clinical infection within 3 weeks; PAC blood cultures each time positive for coagulase-negative staphylococci	–
10	7.3	Osteo-sarcoma	Systemic	131	One episode of systemic clinical infection; PAC blood culture 2× positive for coagulase-negative staphylococci within 3 weeks	–
11	1.0	Rhabdo-myosarcoma	Systemic	157	Two episodes of systemic clinical infection within 4 weeks; PAC blood cultures each time positive for coagulase-negative staphylococci	Coagulase-negative staphylococci
12	0.5	Wilms' Tumour	Systemic	131	Three episodes of systemic clinical infection within 23 weeks; PAC blood cultures each time positive for coagulase-negative staphylococci	–
13	2.4	Neuro-blastoma	Systemic	64	One episode of systemic clinical infection; PAC blood cultures 2× positive for coagulase-negative staphylococci; catheter dislocation	Coagulase-negative staphylococci

AML, acute myelogenous leukaemia; ALL, acute lymphoblastic leukaemia; NHL, non-Hodgkin's lymphoma.

Table 3
Port-related infections in children, review of the literature

Author [reference]	Patient no.	Underlying disease	Total port days	Mean port days per patient	Port-related bloodstream infections	Port-related local infections	Total port-related infection rate per 1000 PAC-days
Wildhaber et al. [8]	91	Cancer	62,488	595	2	4	0.1
Current study	155	Cancer	134,773	738[a]	12	3	0.11
De Backer et al. [9]	46	Cancer	15,024	290	2	0	0.13
Wiener et al. [10]	290[b]	Cancer	189,495	635	Not specified	Not specified	0.14
Munro et al. [11]	134	Cancer	69,342	399[a]	11	1	0.17
Schmidt et al. [19]	41	Cancer	11,138	272	1	2	0.27
Shulman et al. [13]	31	Cancer	7198	232	4	1	0.69
Hollyoak et al. [20]	73	Mainly Cancer	15,251	257	17	0	1.1
Tobiansky et al. [12]	63	Cancer	13,293	211[a]	15	4	1.43
Miller et al. [21]	41	Haemophilia	44,070	930	6	0	0.14
Ljung et al. [22]	53	Haemophilia	49,290	930	9	0	0.19
Santagostino et al. [23]	15	Haemophilia	5426	413[a]	1	1	0.37
Blanchette et al. [24]	23	Haemophilia	15,795	687	11	0	0.7
Aitken et al. [25]	65	Cystic fibrosis	68,220	784	9	0	0.13
Deerojanawong et al. [26]	44	Cystic fibrosis	53,057	700[a]	5	13[c]	0.34
Abdul-Rauf et al. [27]	25	Sickle cell disease	17,444	442[a]	15	0	0.86
Al-Bassam et al. [28]	17	Metabolic diseases	7278	428	6	0	0.82

[a] Median.
[b] No. of devices.
[c] All 13 episodes were isolated local skin infections that required no removal of the port.

phylococcus and *S. maltophilia* were isolated from the explanted PAC, but only *S. maltophilia* from the blood culture.

A summary of previous studies of PAC-related infections in children is presented in Table 3. Compared with similar patient groups, the present study found one of the lowest port-related infection rates (0.11 per 1000 PAC days). However, compared with other patient groups, the port-related infection rate of the present study is low. Notably, the rate of port-related local infections is higher in cancer patients when compared with other patient groups.

4. Discussion

This study, in one of the largest series of paediatric cancer patients with ports observed during an unprecedented period, found one of the lowest port-related infection rates (0.11 per 1000 PAC days) reported when compared with similar patient groups in the literature (Table 3) [8–13,19,20]. Nevertheless, in 8% (13/155) of the patients, removal of the PAC became necessary because of PAC-related systemic or local infection. In one patient with AML (age at diagnosis 0.1 years), PAC removal became necessary three times because of port-related infections.

Few data are available about host factors that contribute to the risk for PAC-related infections [29,30]. In our study, young age appeared to play a role as a predictive factor for PAC-related bloodstream infections. In addition, intensive chemotherapy with periods of severe neutropenia and frequent use of the PAC also influenced the risk for PAC-related bloodstream infections and defined the period we found all PAC contaminations. Local PAC infections requiring PAC removal occurred in all three cases within 36 days after implantation and may represent postoperative infections and/or impaired wound-healing following the start of intensive cytotoxic chemotherapy.

A problem frequently encountered is how to define PAC-related bloodstream infection and when to remove the PAC because of PAC-related infection. Catheter-related bloodstream infection is defined as bacteraemia caused by the same microorganism as cultured from the catheter [29]. Multiple positive blood cultures, quantitative cultures of blood drawn through the catheter with >100 colony forming unit (cfu)/ml and isolation of the same organism from quantitative catheter and percutaneous blood cultures, as well as a differential growth time of >2 h for blood cultures obtained from the catheter compared with those from peripheral blood have been requested for a diagnosis of catheter-related infection [29]. However, in young paediatric cancer patients performing peripheral vein punctures in every episode of fever and neutropenia is rather inconvenient, often clinically not practice and, overall, of little help [31]. Therefore, it is our, as well as a common, policy in paediatrics to culture blood only from the PAC.

With PAC, it has been suggested that the most common route of infection is bacterial contamination of the catheter hub through needle puncture and intraluminal infection [32]. The predominant organisms were coagulase-negative staphylococci, primarily *Staphylococcus*

epidermidis, a common skin commensal that could only have gained access to the port either at the time of PAC insertion or with subsequent needle insertion or catheter handling. However, of greater clinical concern, are the more virulent pathogens eventually causing severe sepsis that may not be treated by catheter removal alone. Rigorous sterile technique is imperative not only at PAC implantation, but in particular when manipulating the port. In contrast to the role of prophylactic antibiotics in the perioperative period that remains controversial [33–36], there is good evidence for full barrier precautions during catheter insertion [37]. In this study, prophylactic antibiotics at surgery were not used. Notably, local infections of the tunnel or pocket were relatively uncommon (3/155 patients) and occurred not in the immediate postoperative period. However, the pocket infections manifesting 25–36 days after PAC implantation in analogy to pacemaker infections occurring within 2 months [38] are thought to result from wound contamination at the operation. The comparison of skin and pocket flora with pacemaker infections has led to the strong hypothesis that overall pacemaker-related infections are mainly due to local contamination during implantation [39]. These findings may well be true in parallel for PAC pocket infections and represent pathogenically different extraluminal infections in contrast to the above discussed intraluminal infections that are thought to prevail in PAC contaminations. Adherence to the evidence-based recommendations for full barrier precautions during insertion may help to minimise such extraluminal infections [37] as well as the correct aseptic puncturing and daily handling of PAC are most critical for the prevention of intraluminal infections. Access of the PAC only by trained physicians may thus have contributed to the low rate of device-related infections observed in our patient cohort.

In general standard of care, removal of a catheter suspected to be infected is strongly recommended, and was the procedure consequently performed in our patients. However, several studies reported successful antibiotic lock therapy of catheter-related infections, particularly bacteraemia due to coagulase-negative staphylococci, by filling the PAC lumen with pharmacological doses of vancomycin for hours or days to kill also the sessile biofilm bacteria [40]. Nevertheless, this salvage approach, especially convenient for totally implanted catheters in avoiding difficult surgical replacement procedures, is associated with a several-fold higher risk for recurrent bacteraemia than after catheter removal [41]. Due to this risk and the observation that catheters in place for more than 2 weeks are most often also infected extraluminally [42] and thus obviously not accessed by antilock therapy, we refrained from using this approach.

In summary, PAC are most important, convenient and relatively safe devices for cancer chemotherapy and patient management in paediatric cancer patients. However, infectious complications with catheter contamination either as catheter-related bloodstream infection (25% of all bloodstream infections) or pocket infection required PAC removal in 8% of patients. Although young age and intensive cytotoxic cancer chemotherapy tend to be risk factors, the prevalence of *S. epidermidis* underlines the critical role of teaching, performance and control of consequently aseptic PAC implantation and handling. Future research must strive to better delineate the molecular mechanisms of microbial adherence to prosthetic surfaces in order to develop new materials intrinsically resistant to contamination, and to design PAC that more effectively deny microbial access.

Conflict of interest

None declared.

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