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Spectrum of external catheter-related infections in children with acute leukemia—Single-center experience

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Abstract
Background: External catheters (ECs) are commonly used in children who are receiving treatment for acute leukemia.
Aims: To study the spectrum of microorganisms and to compare the rates of infection.
Methods: A total of 42 ECs were inserted, including 28 Port-A-Caths, 11 CVC lines and 3 Hickman lines. Single ECs were required for 19 patients (45.2%), whereas 2, 3 and 4 ECs were required in 8, 1 and 1 patients, respectively.
Results: Overall, 37 culture-documented infections were present in 18 (62%) patients who had ECs. Gram-positive microorganisms were identified in 20 cases, Gram-negative microorganisms in 14 cases and fungal infections in 3 cases. Of the 42 devices implanted, 10 out of 28 Port-A-Caths (35.7%), 2 out of 3 Hickman catheters (66.7%) and 9 out of 11 central venous catheters (81.8%) required removal due to infection. The average length of working life for the ports was 330.6 days (range: 40—1043 days). The median rate of complications due to infection was 2.84 infections per 1000 catheter days (interquartile range: −1.55 to 5.8), and the number of infections was correlated with the number of ports (Pearson's $r = 0.51$; $p < 0.05$).

Introduction

External catheters (ECs) are widely used in the management of acute leukemia, although the need, optimal timing of insertion and type of ECs used are variable [1—4]. Individual circumstances

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may vary, but early placement is often desirable, as these patients become neutropenic soon after therapy is begun.

Several types of ECs can be differentiated either by the type of vessel they occupy (i.e. peripheral venous, central venous (CVC), or arterial), their site of insertion (i.e. subclavian, femoral, internal jugular, peripheral, and peripherally inserted central catheter) or their pathway from skin to vessel (i.e. tunneled (Hickman) versus non-tunneled (Port-A-Cath)). The use of ECs and their relationship to blood stream infection rates are influenced by several factors, some of which are patient-related, such as severity of illness and type of illness, or catheter-related, including the condition under which the catheter was placed and the catheter type. Other factors could be institutional, such as bed size, local hygiene and cleanliness, and medical personnel care, among other considerations [5].

This study was undertaken to compare the rates of infection with ECs (Port-A-Cath, central venous catheters, Hickman lines) in children with culture-proven infections receiving treatment for acute leukemia and to study the spectrum of microorganisms cultured in these patients. Although these devices are extremely necessary, they pose a serious risk of increased morbidity and mortality [6]. The increased risk is due to higher incidences of infection, thrombosis, mechanical occlusions and other complications [6—8].

Materials and methods

After obtaining ethical review approval, a retrospective study of the medical records was conducted. The hospital medical record database was searched for all admissions with ICD-10 codes related to acute leukemia. All such records were individually reviewed to identify patients with CVCs, Hickman lines and Port-A-Cath insertions. All inserted Port-A-Cath devices were the lightweight and durable titanium/polyurethane portal reservoir type that were kink-resistant, biocompatible, MRI-compatible, latex-free, PVC-free and radiopaque (Celsite®, Aesculap, Inc., Center Valley, PA, USA). Infections were defined using the Centers for Disease Control (CDC) criteria for catheter-related blood stream infections [9].

This retrospective study covered a two-year period (2009—2010). Incidentally, there were 50 patients with acute leukemia that were enrolled consecutively during the study period. The median age (±SD) was 5 ± 3.3 years. There were 43 patients with acute lymphoblastic leukemia (ALL), whereas 7 cases had acute myelogenous leukemia (AML). All ALL patients were treated using a standard protocol [MRC-UKALL 2003], whereas AML patients received AML-15 chemotherapy according to the current departmental treatment policy for acute leukemia at our institution. Data were collected from patient-specific leukemia protocol flow sheets regarding demographics and blood counts (white blood cells (WBCs), absolute neutrophil count (ANC), hemoglobin and platelets) at the time of diagnosis. Additionally, EC type and the date of EC placement were noted. All devices were inserted in the operating room using a full aseptic technique under fluoroscopic guidance. A chest X-ray was taken to confirm the correct position of the tip of the catheter. Nurses trained in the care of ECs performed dressing changes, which involved skin preparation at the insertion site with an iodine solution and a sterile dressing. Patients suspected of having an EC-related infection had blood cultures taken from both the device and a peripheral vein. Patients were considered to have an EC-related infection if they had a fever of 38 °C or more without any obvious cause or had fever and rigors associated with flushing of the ECs. Line flushing with a dilute heparin solution was undertaken whenever CVC and Hickman lines were accessed.

Statistical analysis

Normally distributed continuous variables were expressed as means ± standard deviations. However, continuous variables that were not normally distributed were expressed as medians with interquartile ranges. Categorical variables were expressed as percentages. Port complications were correlated using Pearson's correlation coefficient. Differences were considered to be significant when $p < 0.05$, and all analyses were performed using SPSS version 15.0 for Windows.

Results

ECs

Table 1 summarizes the patient demographic characteristics. A total of 42 ECs were placed in 29/50 (58%) patients with a total period of 12,271 catheter days. The average length of working life for the ports was 330.6 days (range: 40—1043 days) (Table 2). In 28, 11 and 3 patients, single or multiple Port-A-Caths, CVCs or Hickman lines were inserted, respectively. Single ECs were required for 19 patients (45.2%), whereas 2, 3 and 4 ECs were required in 8, 1 and 1 patients, respectively.

Table 1 Demographic and clinical characteristics of patients with external devices (*n* = 29).

Age (years)	
Mean ± SD	5.5 ± 4.0
Range	1.0—13
Male sex, *n* (%)	14 (48)
Female sex, *n* (%)	15 (52)
Type of disease	
ALL Pre-B ALL, *n* (%)	18 (62)
T-cell ALL, *n* (%)	2 (7)
Relapsed ALL, *n* (%)	2 (7)
Infant ALL, *n* (%)	1 (3)
AML, *n* (%)	6 (21)
Type of port	
Port-A-Cath (%)	28 (67)
CVC (%)	11 (26)
Hickman (%)	3 (7)
No. of ports (%)	42 (100)
One port, *n* (%)	19 (45.2)
Two ports, *n* (%)	8 (38.1)
Three ports, *n* (%)	1 (7.1)
Four ports, *n* (%)	1 (9.5)
Duration of port, days (range)	331 (40—1043)
No. of organisms	
All cases, *n* (%)	37 (100)
Gram-positive, *n* (%)	19 (51.4)
Gram-negative, *n* (%)	15 (40.5)
Fungal, *n* (%)	3 (08.1)

Infections

Overall, 37 culture-documented infections were found in 18 (62%) patients who had ECs. There were no organisms identified in 11 (38%) cases, whereas 12 (41%) patients grew 1 organism, 1 (3.5%) case each grew 2 and 3 organisms, 2 (7%) cases each grew 4 organisms and 2 (7%) cases each grew 6 organisms. Most cases with CVCs showed infection with multiple organisms. Infections developed in 2 out of 3 cases with Hickman catheters.

Gram-positive microorganisms were identified in 54.1% of the positive cultures, Gram-negative microorganisms in 37.8% cultures and fungal infections in 8.1% cultures (Table 3). The Gram-positive organisms isolated were coagulase-negative *Staphylococcus* (11), *S. aureus* (2), *Bacillus* spp. (2) and one each of *Streptococcus hemolyticus*, *Streptococcus salivarius*, *Streptococcus viridians*, *Micrococcus* spp. and *Staphylococcus epidermidis*. The Gram-negative organisms isolated were *Klebsiella pneumoniae* (5), *Escherichia coli* (4), and one each of *Pseudomonas aeruginosa*, *Ps. putida*, *Acinetobacter baumannii*, *Haemophilus influenzae* and *Enterobacter cloacae*.

Outcomes

Risk stratification in acute leukemia is important for selecting the appropriate therapy and predicting outcomes. Patients are generally classified as low (standard) risk, intermediate and high risk based on demographics, laboratory markers of tumor burden and cytogenetic features. Low-risk (standard) cases have favorable demographics and laboratory features with no cytogenetic abnormalities. Intermediate-risk patients have unfavorable demographics and laboratory features but have no abnormal cytogenetic features. High-risk patients have unfavorable demographics and laboratory features, present cytogenetic abnormalities and have poor responses to initial therapy.

Of the 42 devices implanted, 10 out of 28 (35.7%) Port-A-Caths, 2 out of 3 (66.7%) Hickman catheters, and 9 out of 11 (81.8%) CVCs required removal due to infection. Twenty-four children were stratified as standard risk. In this group, 6 patients had ECs (all Port-A-Caths), but only 4 became infected; only 1 EC had to be removed. Twenty-six children were stratified as intermediate- and high-risk patients, with a total of 36 EC insertions. In this group, 22 Port-A-Caths were inserted, 14 of which developed infections, with 10 ports needing removal due to infection. Because of infection, 9 out of 11 CVC lines and 2 out of the 3 Hickman lines had to be removed. Thus, patients with high- and intermediate-risk disease had more EC insertions and more infections than patients with standard-risk disease.

Discussion

ECs such as Port-A-Caths, CVCs and Hickman lines are extremely useful devices for patients who require continuous, uninterrupted long-term venous access during chemotherapy schedules for the management of acute leukemia. However, these devices are often associated with complications that include occlusion, infection and thrombosis [1,2,10,11].

In our hospital, the Hickman catheters used are dual-lumen and are not coated with antimicrobials, antiseptics or nanoparticles. The central venous catheters are either double- or triple-lumen and are not coated with any antibiotics. We restrict the use of one lumen for blood and blood products, whereas the other lumen is used for administering antibiotics, crystalloids and colloids and parenteral nutrition. However, as a hospital policy, the third lumen, if available, is reserved for parenteral therapy in patients who require it. The interval

Table 2 Correlation of port infections with port survival times in 29 patients.

Type of port	No. of ports	No. of organisms	No. of days of port 1	No. of days of port 2	No. of days of port 3	No. of days of port 4	Total no. of days with port	No. of infections/1000 port days
PC	1	0	365				365	
PC	1	0	730				730	
PC/CVC	2	0	256	65			321	
PC	1	1	1043				1043	0.96
PC	1	0	1122				1122	
PC	1	0	1078				1078	
H	1	0	130				130	
PC	1	1	178				178	
PC/CVC	2	2	100	96			196	10.2
PC/H	2	1	108	54			162	6.17
PC/H	2	6	107	40			147	40.8
PC	1	0	789				789	
PC	1	0	809				809	
PC	1	1	723				723	1.38
PCX2/CVC	3	3	66	100	91		257	11.67
PCX2	2	1	384	200			584	1.71
PC	1	0	81	61			142	
PC	1	0	586				586	
PC/CVC	2	6	26	21			47	127.65
CVC	1	1	299				299	3.34
PC	1	1	437				437	2.28
CVC	1	0	248				248	
PC	1	1	711				711	1.4
PC	1	1	332				332	
PC	1	1	352				352	2.84
CVC'sX2/PCX2	4	4	29	3	45	22	99	40.4
PC	1	1	177				177	5.64
CVCX2	2	4	18	22			40	100
PC/CVC	2	1	107	60			167	5.98
Total	42	37	11,391	722	136	22	12,271	
			Average no. of days/port = 330.61 (range 40—1043)					

PC, Port-A-Cath; CVC, central venous catheter; H, Hickman catheter.

between port needle puncture was usually between 5 and 7 days, and needles were always removed at discharge or when the use of parenteral therapy was no longer needed. If the catheter was removed due to infection, a new catheter was inserted. However, if there was no further need of parenteral therapy, we chose not to reinsert another catheter. Our data certainly indicate that the presence of current infection was a high risk for re-infection. However, we needed to reinsert a port/catheter because of poor venous access when the patients were on intense chemotherapy and/or supportive therapy. We do not administer prophylactic antibiotics to these patients. Antibiotics are only started after suspicion or if evidence of culture-proven infection is available. Despite being on antibiotics, we observed that approximately one-third of the patients in our study cohort developed infection with a different organism (Table 2).

The most important cause for the removal of ECs in this cohort of patients was infection, similar to data presented in other studies [1,2,10,11]. Overall, infections in ECs were observed at a rate of 2.84 infections per 1000 catheter days (interquartile range: 1.55—5.8), and the number of infections was correlated with the number of ports (Pearson's $r = 0.51$; $p < 0.05$). A literature review shows that infections in ECs vary from 1.8 to 3.4 infections per 1000 catheter days [4,11]. Combined data from 8 studies involving 320 pediatric oncology patients revealed an infection rate for ECs of 2.2 infections per 1000 catheter days [12].

Most of the CVC and Hickman lines and 35% of Port-A-Cath devices had to be removed due to inter-current infections that were documented by positive cultures. This outcome likely reflects the combination of nursing care and patient hygiene and needs to be improved by strict implementation

Table 3 Numbers and types of organisms isolated during episodes of infection.

Isolated microorganisms	No.	Port-A-Cath	Hickman	CVC line
Gram-positive ($n = 20$, 54.1%)				
Staphylococcus aureus (MRSA)	2	2		
Staphylococcus epidermidis	1			1
Coagulase-negative *Staphylococcus*	11	8	1	2
Staphylococcus hemolyticus	1			1
Streptococcus salivarius	1		1	
Streptococcus viridans	1			1
Micrococcus species	1	1		
Bacillus spp.	2	2		
Gram-negative ($n = 14$, 37.8%)				
Klebsiella pneumoniae	5		1	4
Escherichia coli	4	1		3
Pseudomonas aeruginosa	1	1		
Pseudomonas putida	1			1
Acinetobacter baumannii	1			1
Enterobacter cloacae	1	1		
Haemophilus influenzae	1	1		
Fungi ($n = 3$, 8.1%)				
Candida krusei (*Issatchenkia orientalis*)	1			1
Candida tropicalis	1	1		
Candida kefyr	1			1
Total	37	18	3	16

of the recommended guidelines [5]. The number of infections per 1000 port days was lowest in patients with Port-A-Caths, ranging between 0.96 and 5.64; Hickman lines had an intermediate infection incidence that ranged from 6.17 to 40.8 per 1000 port days. However, infection incidence was significantly high in CVCs, and ranging from 53.3 to 127.65 per 1000 (Table 2).

The total number of port days in patients ($n = 11$) who did not grow microorganisms in culture was higher (6194) than in patients ($n = 18$) with positive cultures (5197), but this difference was not statistically significant. Moreover, only 12 ports were used in the former group (ratio 1.09), in contrast to 30 ports in the latter group (ratio, 1.67). It is apparent that these numbers indicate the presence and effects of infection. However, because of the small sample size, the differences are not statistically significant.

In the 5 patients who were managed with a single port for more than 2 years, only 1 patient grew a single organism (blood culture), which reflects the excellent port care employed by the team looking after these patients. Current guidelines/recommendations for management of devices indicate that devices survive longer if they are handled by experienced staff from the same center using standardized protocols of care at all times [6].

Staphylococcal infection seems to be the most common type reported in the literature regarding EC infections, with a prevalence of almost 90% [4,11,12]. *Staphylococcus* was also the most prevalent microorganism isolated in our study, but overall, Gram-positive organisms only accounted for 54.1% of infections; a significant proportion of Gram-negative infections was also identified in this study (37.8%).

Two patients developed polymicrobial infections with 6 organisms each (Table 2). Both of these patients were high-risk ALL cases that responded poorly to chemotherapy; 1 patient required bone marrow transplantation. One patient who needed two lines (a Hickman line (107 days) and a Port-A-Cath (40 days)) developed mostly Gram-positive infections with Coagulase-negative *Staphylococcus* (2), *S. salivarius*, *S. aureus* and *Micrococcus* species. Another patient who also required two lines (a CVC (26 days) and a Port-A-Cath (21 days)) developed infections mainly with Gram-negative organisms, namely *K. pneumoniae*, *A. baumannii* and *Ps. putida*, along with *Candida krusei* (*Issatchenkia orientalis*). The microbial patterns were quite distinct in these two cases, with polymicrobial infections with Port-A-Cath and Hickman lines favoring Gram-positive infections, and CVCs favoring Gram-negative and fungal infections. Furthermore, the CVC needed to be removed from the latter patient within a short period of time (26 days).

Overall, multiple organisms were identified in approximately one-third of infections (37.5%), with most instances in CVCs and Hickman lines. This finding is likely a reflection of the poor nursing care and patient hygiene, which are essential for preventing and reducing such infections. Importantly, most of these ECs had to be removed. In contrast, Port-A-Caths with fewer infections have the advantage of decreased care requirements for patients' families, cause less self-consciousness, allow for ease of bathing and are not prone to accidental removal.

Conclusions

The study shows that although ECs in patients with acute leukemia help in facilitating the delivery of chemotherapy and parenteral support, especially during the neutropenic phase, the catheters increase the risk of developing infections. Gram-positive organisms, especially *Staphylococcus*, are the most predominant organisms involved, but Gram-negative organisms were also identified in significant numbers in this study. CVCs and Hickman lines showed higher infections requiring catheter removal, reflecting a lack of adherence to recommended guidelines and demonstrating the importance of nursing care. Port-A-Caths were much less likely to be infected. Overall, the practice of good nursing care and recommended infection prevention guidelines should be implemented and will go a long way in reducing these complications.

Conflict of interest

The authors have no conflicts of interest or funding to disclose.

Ethical approval

Not required.

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