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Neutropenia at the Time of Subcutaneous Port Insertion May Not be a Risk Factor for Early Infectious Complications in Pediatric Oncology Patients.

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NEUTROPENIA AT THE TIME OF SUBCUTANEOUS PORT INSERTION MAY NOT BE A RISK FACTOR FOR EARLY INFECTIOUS COMPLICATIONS IN PEDIATRIC ONCOLOGY PATIENTS

By

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ABSTRACT

The risk of infection associated with subcutaneous port (SQP) placement in patients with neutropenia remains unclear. We reviewed the rate of early infectious complications (<30 days) following SQP placement in pediatric oncology patients with /without neutropenia (absolute neutrophil count (ANC)<500/mm^3).

Baseline characteristics and infectious complications were compared between groups using univariable and multivariable analysis.

A total of 614 SQP were placed in 542 patients. Compared to non-neutropenic patients, those with neutropenia were more likely to have leukemia (94% vs 50%), pre-operative fever (22% vs 5%), pre-operative infection (19% vs 9%), and were younger (81 vs 109 months) (p values <0.01).

After adjusting for fever and underlying-disease there was a non-significant association between neutropenia and early post-operative infection (OR 2.42, 95% CI 0.82-7.18, p=0.116). Only pre-operative fever was a predictor of infection (OR 6.09, 95% CI 2.08-17.81, p=0.564).

Neutropenia may not be a predictor of early postoperative infection following SQP placement.

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KEY TO SYMBOLS AND ABBREVIATIONS

ANC	Absolute Neutrophil Count
BMI	Body Mass Index
CLABSI	Catheter Associated Blood Stream Infection
DLTC	Double Lumen Tunneled Catheter
IJ	Internal Jugular Vein
IR	Interventional Radiology
PICC	Percutaneously Inserted Central Catheter
SLTC	Single Lumen Tunneled Catheter
SQP	Subcutaneous Port
WBC	White Blood Cell

CHAPTER 1

INTRODUCTION

Tunneled central venous catheters are essential to the management of a variety of hematologic and solid tumor malignancies.[1] These devices allow long-term vascular access that permits the administration of chemotherapy, frequent blood sampling, and the administration of antibiotics, supportive medications, and total parenteral nutrition, thus making them indispensable.[2] The choice of which indwelling central venous catheter (double lumen tunneled catheters (DLTC), single lumen tunneled catheters (SLTC), and subcutaneous ports (SQP)) is multifactorial. Patient diagnosis will often dictate the choice of which tunneled device to use. Certain oncologic diagnoses may require bone marrow transplantation and/or the need for multiple chemotherapeutic agents that are not compatible with one another. This may necessitate a dual lumen device and result in the patient receiving a DLTC.[3]

The size of the patient and lack of sufficient subcutaneous tissue may preclude the insertion of a SQP. As a result, these patients (such as infants, for example) usually receive SLTC. Parent and patient preference will often times guide which tunnelled device we use. The totally implantable SQP offers the advantage of being completely covered, and when not in use, the patient may shower, and swim, and engage in most regular activities. Often times, this device is chosen for improved quality of life. A less desirable feature of this central line however, is that each time it is accessed a needle must be inserted through the patient's skin and subcutaneous tissue overlying the port. This may cause pain, and unnecessary anxiety in some patients. Ultimately

the repeated needle sticks may overshadow the potential benefit of a completely implantable device. Finally, some centers use severe neutropenia (an absolute neutrophil count (ANC) of less than 500 per mm^3) as an exclusion criterion for insertion of SQP.[3]

Many pediatric oncology patients present with neutropenia at diagnosis, or experience this event throughout their treatment with cytotoxic chemotherapy. Neutrophils are a type of white blood cell responsible for identifying and eradicating foreign pathogens as well as killing microbes.[4] The significance of neutropenia when selecting which tunneled central venous access port to use is unclear and will be summarized in this literature review.

As with all invasive access devices, there is potential for complications. Early infection, those occurring within 30 days of catheter insertion, is the most notable and frequent reported complication to occur in 8-22% of cases.[5-7] Subcutaneous ports are totally implantable subcutaneous devices and are associated with the lowest rate of infectious complications among central venous catheters.[8] A prospective nonrandomized study performed by Ross and colleagues examined complications in totally implantable vascular devices (SQP) and externally exiting catheters (DLTC/SLTC). During the study interval 50 ports and 49 external catheters were inserted. There were 15/41 (37%) complications in the external catheter group as compared to 7/50 (14%) in the SQP group, p=0.02.[9] Despite the trend towards less infectious risk with totally implantable vascular devices, the consequence of infection may be more significant. Catheter related infections, port site, or tunnel site infections, and surgical site complications often necessitate removal of the SQP under general anaesthetic and delay in therapy. Furthermore, implanted central venous catheter infections are associated with a significant amount of morbidity and occasionally mortality.[10,11] Siempos et al. conducted a meta-analysis of comparative studies that reported on mortality of intensive care unit adult

patients with central line-associated bloodstream infection (CLABSI) and found that the presence of CLABSI is associated with a higher mortality in critically ill adult patients after matching for severity of illness (OR 1.70, 95% CI 1.00-2.90).

Efforts have thus been made to optimize timing for insertion of SQP to minimize the risk of early postoperative infection. There is currently no standard protocol with regards to the placement of SQP in the setting of neutropenia and therefore practices vary widely between centers. Insertion may occur at the time of initial diagnosis, beginning of remission induction therapy, or following resolution of neutropenia.[2,3,12,13]

Gutierrez et al. implemented an institutional protocol whereby children with neutropenia and hematologic malignancies were excluded from placement of tunneled central venous catheters until neutropenia resolved. Patients were bridged with a percutaneously inserted central catheter (PICC) line in the interim. They conducted a retrospective study comparing the 100-day post-insertion outcomes with neutropenic patients prior to the implementation of the ANC exclusion protocol and those after the implementation. They demonstrated that there was a strong trend towards a lower incidence of removal for infection following initiation of the protocol, although this was not statistically significant (4.1% [13/314] vs. 0.8% [1/126], p=0.07). The authors noted that SQP were more likely than DLTC or SLTC to be removed within 100 days for all causes. The logistic regression that was conducted identified neutropenia as the only independent risk factor for early catheter removal. Interestingly, they also noted that the insertion of PICC lines was not without some morbidity, with seven (15.6%) requiring removal due to infection (3), deep venous thrombosis (2) and catheter fracture (2).[12] However, this study was limited due to only having assessed patients with hematologic malignancies, and including patients receiving all forms of tunnelled central venous catheters.

Waiting for neutropenia to resolve prior to definitive line placement may result in a delay in therapy and multiple unnecessary procedures. There is currently no consensus guiding placement of SQP in pediatric oncology patients with neutropenia. The literature presents conflicting opinions, with some studies documenting increased infectious risk,[12,13,14-16] and others demonstrating no significant increased risk.[2,17,18]

A retrospective review of 350 children with acute lymphoblastic leukemia, and aplastic anemia found that patients with neutropenia (ANC<500/mm^3) at the time of catheter placement had an increased risk of catheter removal within 100 days of placement secondary to infection (12.4% vs. 0.9%) compared to those without neutropenia.[13] Additionally, in this same series, one patient in the neutropenia group died of infectious related SQP complications compared to no patients in the non-neutropenic group. They concluded that, when possible, central venous catheters, particularly SQP, should be avoided in the presence of neutropenia. This retrospective review only included children with a hematologic malignancy, and included all forms of tunnelled central venous access.

Shaul et al. performed a retrospective review of all patients undergoing tunnelled central venous catheter insertion at a single institution. They looked at those who developed fever and positive blood culture drawn through the line within 45 days of insertion and compared them with control patients (two controls per case). This study found that among the 473 lines that were placed, early infections developed in 53 patients (12%). Neutropenia (defined in their study as ANC <1000/mm3) was found in 16/53 infected patients compared with 8/106 controls (OR 5.30, 95% CI 1.91-15.04, p=0.004). Interestingly, preoperative antibiotics were given to only 25/53 infected patients compared to 72/106 controls (p=0.02). They concluded that neutropenia and failure to administer prophylactic antibiotics are risk factors for the development of early

tunneled catheter infections in pediatric patients.[16] This study was limited in that the study population was not confined to the pediatric oncology population. Further, the statistical analysis showcased in the manuscript did not account for possible confounding variables.

Junqueira et al performed a retrospective study of children with leukemia undergoing SQP insertion and found results contradictory to the previous authors. Early (<30 days) post procedure complications were reviewed. They defined neutropenia as an ANC <500mm^3. They found that in 192 ports, the incidence of catheter associated infection did not differ between neutropenic and non-neutropenic patients (15% vs. 24%, p=0.137).[2] This study may be limited by its low event rate, and failure to account for confounding in the statistical analysis.

Hoss et al. conducted a retrospective review of 183 pediatric oncology patients who underwent SQP placement at a single centre. They compared patients with severe neutropenia (ANC<500/mm^3) to those with ANC>=500/mm^3. The primary outcome of this study was the presence of documented infection within the first 30 days post-procedure. They found that the incidence of early infection was not significantly different between groups (12.5% neutropenia vs. 4.5% non-neutropenia, p=0.08). They did find, however, that the rate of CLABSI per 1000 catheter days was higher for patients with severe neutropenia (p=0.045). Despite this, most infections were able to be treated without SQP removal and the removal rate was not different between groups (2.5% vs. 2.7 %, p=0.32).[17] They concluded that port placement in patients with severe neutropenia can be performed without an increased incidence of removal for infection. This study was most limited by a small event rate (n=14).

The optimal timing of placement of a SQP in pediatric oncology patients, especially in the setting of neutropenia, has been widely studied, and the findings in the literature vary. This may be secondary to variation in the definition of severe neutropenia, or the patient population studied (those with hematologic malignancies only vs. all pediatric oncology patients). Results may differ as a result of small sample size and failure to consider confounding within the analysis.

Therefore, the purpose of this study was to examine the association between neutropenia (i.e., the exposure) and the development of early post-operative infectious complications) 30 days following the initial procedure) (i.e., outcome) in pediatric oncology patients who underwent SQP insertion.

Secondary objectives included documenting the incidence of early post-operative infectious complications as well as to identify risk factors associated with SQP-related infectious complications. Furthermore, we aim to describe the type of infectious complications that occur, along with resulting intervention, if required, such as catheter removal, and antibiotics. We aim to develop guidelines when considering optimal timing of SQP placement.

CHAPTER 2

METHODOLOGY

Patients

An Institutional Review Board-approved retrospective review was performed (Appendix). Electronic medical records of all pediatric oncology patients undergoing SQP placement at St Jude Children's Research Hospital between January 2013 and December 2016 were reviewed.

Port placement

All procedures were performed under sterile technique in the operating room or in the interventional radiology suite. Prophylactic antibiotics (intravenous cefuroxime (50mg/kg) or clindamycin) were administered to all patients within 30 minutes of skin incision. All catheters were inserted percutaneously under general anaesthesia. Ultrasound guidance was used to guide internal jugular vein access, and anatomic landmarks were used to guide the subclavian approach. The choice of vessel accessed was determined by the surgeon, or interventional radiologist placing the line. Subcutaneous ports were either tunnelled and placed on the chest wall, or placed in the sub clavicular position with minimal tunnel. Correct position was confirmed using fluoroscopy during the procedure and a standard chest radiograph was obtained immediately following port placement. The choice of diameter of catheter tubing was determined by the weight of the patient, favoring 6.6 French catheters for patients < 30 kg.

Post-operative subcutaneous port care and maintenance were performed according to the nursing policy and procedure manual of this institution. While not in use, the subcutaneous port was flushed with heparin (100 units/ml). While in use, the Huber needle of the port was changed weekly under sterile technique. Sterile line dressings were applied as per hospital policy.

Data collection

Electronic medical records of all pediatric oncology patients undergoing subcutaneous port placement were reviewed. We recorded age at insertion, body mass index (BMI), underlying disease (i.e., leukemia, lymphoma, or solid tumor), history of previous central catheter placement, documented preoperative infection (within two weeks of procedure), presence of fever within 24 hours of port insertion, date of initiation of chemotherapy, location of port placement, size of catheter tubing, and service placing subcutaneous port (interventional radiology vs. general surgery). Most recent laboratory values were also collected prior to port insertion and included: white blood cell count (WBC), platelet count, hemoglobin, glucose, and absolute neutrophil count (ANC). Baseline characteristics and infectious complications were compared between neutropenic and non-neutropenic patients.

In this study, the exposure of interest was neutropenia, which was defined as ANC<500/mm^3. ANC values were recorded as continuous measures but then categorized into a dichotomous variable (<500/mm^3 vs. >= 500/mm^3) for data analysis.

The primary outcome was early infectious complications (i.e., within 30 days of SQP placement). This was further defined as: 1) bacteremia (i.e, isolation of a pathogen from a blood culture drawn through the lumen of the SQP [19-21]); 2) surgical site infection (i.e.,

presence of erythema, induration, and/or tenderness or evidence of purulent discharge at the surgical incision); or 3) tract infection (i.e., presence of erythema, induration, and/or tenderness within 2 cm of the port or catheter tubing.[22,23]

Statistical analysis

Descriptive statistics were calculated for patient characteristics with means and standard deviations for continuous variables and frequency (percentage) for categorical variables. All calculations were done using SAS software version 9.4.[24] All tests were 2-sided and the significance level was set at a p-value of less than 0.05. A t-test was performed to compare continuous variables, and a Pearson chi-square test was performed to compare categorical variables between patients with and without neutropenia.

Logistic Regression Analysis

The association between neutropenia and early post-operative infection rate was examined using logistic regression analysis. We dichotomized ANC <500/mm^3 (neutropenia) and >=500/mm^3 (non-neutropenia). Clinical investigators pre-selected five potential confounding variables that were assessed in this model: the presence of preoperative fever (within 24 hours of port insertion), if the patient had received preoperative chemotherapy, history of previous central line, underlying disease (leukemia, lymphoma, or solid tumor) and patient's body mass index (BMI). Underlying disease (hematologic malignancy vs. solid tumor) was pre-selected as the only potential effect modifier.

The presence of confounding effects was assessed by the change in estimate procedure and used to determine the final model. Variables were entered into the model one at a time. If the adjusted odds ratio changed by greater than ten percent, the variable was retained. Otherwise, the variable was removed from the model. Effect modification was assessed by including a multiplicative interaction term in the model.

To identify other potential risk factors for the development of early post-operative infectious complications following SQP insertion, a univariable logistic regression analysis was performed. Fourteen pre-selected variables of interest were examined: preoperative fever, underlying disease, location of catheter (internal jugular vein vs. subclavian vein), location of port (chest wall vs. sub clavicular), chemotherapy use prior to port insertion, service placing the SQP (interventional radiology vs. surgery), history of previous central line, history of infection within two weeks of SQP insertion, body mass index (BMI), age, gender, glucose, hemoglobin, catheter size (diameter). All variables with a p-value <0.3 in the unnvariable analyses were entered into the multivariable model and backwards selection was used to identify potential predictors of infection. All variables with a p-value <0.25 were retained in the multivariable model. Odds ratios and 95% confidence intervals were determined. All calculations were done using SAS software version 9.4.[24]

CHAPTER 3

RESULTS

Patients

In our study period, 614 subcutaneous ports were placed in 542 pediatric oncology patients. The majority (79%) of ports were first-time insertions with the remainder being second (16%), third (5%), or forth (1%) devices. Characteristics of the 614 ports are summarized in Table 1. There were 272 (44%) ports were placed in children with solid tumors and 342 (56%) were placed in children with a diagnosis of leukemia or lymphoma. The study cohort included 79 ports (13%) placed in neutropenic patients and 535 (87%) placed in those who were non-neutropenic. Statistically significant baseline differences between non-neutropenic and neutropenic patients included age (mean age 109 vs 81 months), presence of fever within 24 hours of port placement (5% vs 22%), underlying disease: leukemia (50% vs. 6%), and solid tumor (50 vs 96%), respectively. The following variables were also found to be significantly different between the two groups: chemotherapy prior to SQP insertion (35% vs. 23%), previous central line insertion (40% vs. 20%), hemoglobin (10.9, 9.0 g/dL), and rate of infectious complications (2% vs. 9%), respectively.

Infections

Characteristics of the 18 post-operative infections are summarized in Table 2. No patient in our data set had more than one infection. Seven (9%) patients in the neutropenic group developed

early post-operative infection compared to 11 patients (2%) in the non-neutropenic group. The median time to infection was 14.5 days following subcutaneous port placement (range, 2 – 30 days). Most patients developed bacteremia (67%), with the remainder having port site infection (22%) or the presence of both port site infection and positive blood culture (2%). The most common organism isolated was *Staphylococcus aureus* (28%). The majority of patients (78%) were neutropenic at the time of developing infectious complication. Treatment of infectious complications included antibiotics only (56%), surgery only (i.e, removal of subcutaneous port, 11%), and both surgery and antibiotics (33%). The majority of infectious complications resulted in a delay of therapy (96%).

Regression Analysis

Baseline characteristics and infectious complications were compared between neutropenic and non-neutropenic patients using multivariable logistic regression. No interaction was found between neutropenia and underlying disease (p=0.97). The multivariable regression model did find the presence of preoperative fever and disease (solid tumor vs. leukemia/lymphoma) to be significant confounding variables (Table 3).

The model was therefore expressed as:

$$Y \text{ (log odds of having infection)} = \alpha + \beta 1(\text{NEUTROPENIA}) + \beta 2(\text{DISEASE}) + \beta_3(\text{FEVER})$$

After adjusting for underlying diagnosis (disease) and the presence of fever within 24 hours of port placement, the increased risk of early post operative infection in the presence of neutropenia was no longer significant (OR 2.42, 95% CI 0.82-7.18, p=0.1106).

Univariable logistic regression was used to identify potential risk factors for early post-operative infection following SQP placement. These results are summarized in Table 5. Pre-operative fever was found to be associated with increased risk of infection (OR 7.78, 95% CI 2.76-21.92). A diagnosis of hematologic malignancy (leukemia/lymphoma) was similarly found to be associated with increased risk of infection (OR 3.92, 95% CI 1.12-13.69, p=0.0321). The initiating of chemotherapy prior to SQP placement was found to be associated with a lower risk of post-operative infection (OR 0.42, 95% CI 0.12-1.48, p=0.1780). Finally, higher hemoglobin levels were also found to be associated with decreased risk of infection with a 25% decrease in risk for every on unit increase in hemoglobin. (OR 0.75, 95% CI 0.58-0.96, p=0.0251).

AfA second multivariable logistic model was constructed to examine the association between these selected risk factors and early post operative infection followed by a Wald test for the overall effects of ANC on infection. This model relied on backward elimination on all pre-selected risk factors. This process found two significant variables (fever and underlying disease). A multivariable model was thus created adjusting for these two variables; the model can be summarized in the equation bellow and the results are summarized in Table 6.

$$Y \text{ (log odds of having infection)} = \alpha + \beta_1 \text{fever} + \beta_2 \text{underlying disease}$$

The presence of fever within 24 hours of SQP placement was found significantly associated with an increased risk of infection (OR 6.09, 95% CI 2.08-17.81, p<0.0010) after adjusting for underlying disease (OR 4.67, 95% CI 2.08-17.81, p=0.0564).

CHAPTER 4

DISCUSSION

Overall five-year survival for pediatric malignancies has increased dramatically over the past 50 years. Cure rates for leukemia now approach 80% .[25] This is largely secondary to improved chemotherapeutic strategies as well as organizing multi-centered trials and standardized treatment protocols. The use of tunneled central venous catheters is a mainstay of treatment of most pediatric malignancies. It provides a safe route for delivery of these life-saving drugs, a method of obtaining frequent blood tests, providing supplementary nutrition, as well as supportive medication. Implanted central venous infections are associated with increased patient morbidity and mortality[13,26] and may also necessitate removal of the line. In an effort to minimize the morbidity in this vulnerable population, the use of central lines in pediatric oncology patients has been extensively studied. Unfortunately, the literature to date has provided conflicting results. The objective of our study was to examine the relationship of preoperative neutropenia on the early postoperative infection rate following subcutaneous port placement. Secondly, we sought to identify other variables that may increase the likelihood of infection following SQP placement.

The optimal timing of placement of tunneled central venous lines has been an area of interest in several studies, specifically with regards to preoperative neutropenia. Neutrophils are cells responsible for clearing the blood of foreign material (including microbes). It is well established that the chance of infection is directly proportional to the severity and duration of neutropenia .[27]

Historically, placement of SQP (and other invasive procedures) in the setting of severe neutropenia has been discouraged due to the potential increased risk of serious infections and wound healing.[16] Some studies have demonstrated that neutropenia (ANC<=500-1000/mm^3) at the time of tunneled central venous line insertion has been associated with an increase in post operative infection and line removal and therefore recommend delaying central line placement until count recovery.[28,29] Conversely, other studies have demonstrated that neutropenia is not a significant risk factor for infection following central line placement.[3,17] Neutropenia is a common occurrence in the setting of cancer, both at the time of diagnosis and throughout therapy. Some authors argue that although many oncology patients present with normal or elevated neutrophil counts, these cells are likely immature and/or dysfunctional. Their ability to fight infection therefore remains uncertain.[30] The importance of neutropenia in the setting vascular access remains controversial. In this study, we have demonstrated that, after adjusting for pre-operative fever and underlying disease, while there appears to be an associated between neutropenia and early post operative infection following SQP placement (OR 2.4, 95% CI 0.82-7.18), this association does not reach statistical significance (0.1106). This may be due to the low event rate observed in this study (18/614). This finding is in keeping with several other studies that examined early post-operative wound infections in the setting of neutropenia following placement of tunneled lines.[3,17]

Other factors that have been studied with regards to infectious risk and central line placement include site of line placement (internal jugular vein versus subclavian vein), type of catheter used (subcutaneous port versus tunneled central access devices), age of patient, and the presence of preoperative fever. We found that the choice of vessel (internal jugular vein versus subclavian vein) did not influence infectious risk (OR 1.18, 95% CI 0.41-3.36, p=0.7570). This is in

keeping with the literature.[31,32] Many studies have found that SQP are associated with the least amount of infectious rate among central venous catheters.[8] Our study only examined patient following SQP placement and so we did not explore the effect of the type of device on risk of infectious complications.

Historically, tunnelled central venous catheters were placed exclusively by the surgical department. Over the past 15 years, however, there has been a shift in practice, wherein at many centers these lines are now placed by the interventional radiology department. Some studies have found that lines placed by the radiology department have been associated with decreased cost and morbidity.[33,34] Our study found that the service placing the SQP (interventional radiology versus surgery) was not a risk factor for early infection (OR 1.23, 95% CI 0.40-3.79, p=0.7185). This difference may be secondary to a more standardized approach to line care both at the time of insertion (initial dressing) and post-operative management.

Several studies have found that the age of the patient at time of tunneled central venous line placement may pre-dispose them to post-operative complications.[17,35] These studies found an increased risk of infectious complications following line placement in children less than 10 years of age. Our study did not find age to be a predictive factor for early post-operative infection following SQP placement (OR 1.00, 95% CI 1.00-1.00, p=0.3795).

Our study did find that for every unit increase in hemoglobin, the odds of developing a post-operative wound infection decreased by 0.75 (OR 0.75, 95% CI 0.58-0.96, p=0.0251). This is not surprising, given the established literature demonstrating an association between anemia and increased risks of postoperative complications (including infection). This may be secondary to lower oxygen carrying capacity and the subsequent lower oxygen tension in tissues resulting in poorer wound healing and in decreased local immunity.[36,37]

We also found, in the univariable regression, that patients with a diagnosis of leukemia or lymphoma appeared to be almost four times more likely to develop an early post-operative infectious complication as compared to patients diagnosed with a solid tumor (OR 3.92, 95% CI 1.12-13.69, p=0.0321). This relationship was maintained in the multivariable analysis though become non statistically significant (OR 4.67, 95% CI 2.08-17.81, p=0.0564). This may be understood by the fact that, in general, the hematologic malignancy population presents more systemically unwell, and often with profound bone marrow suppression, as compared to the solid tumor group. Further, both groups differ significantly with regards to timing of initiation of chemotherapy as well as the types of chemotherapeutic agents used to treat the underlying disease. Finally, the observed increase risk of infection associated with the leukemia/lymphoma group may be exaggerated given our low event rate (only 3 infections occurred in solid tumor patients with neutropenia), this is apparent by the wide confidence intervals observed.

The importance of pre-operative fever in the absence of an isolated pathogen and the risk of post operative wound infection following line placement in the pediatric oncology patient remains poorly defined. Fever is not uncommon in children with acute lymphoblastic and lymphocytic leukemia. It is hypothesized to be secondary to the release of cytokines from leukemic cells, the administration of certain drugs, or even the transfusion of blood products.[38] While fever in an oncology patient is often multifactorial, and may not be an indication of acute infection, it has been found to be associated with a higher rate of post-operative infections following SQP insertion.[2] Similarly, our study demonstrated a significantly increased risk of infection following SQP placement in patients that had a documented fever in the 24 hours preceding surgery (OR

6.09, CI 2.08-17.81, p=0.0010). This should be interpreted with some caution, given the wide confidence intervals.

In our study period, the incidence of early post-operative infections following SQP placement was 2.9% (18/614). This is comparable to the incidence of infections found in the literature (0.7-12.6%).[11] Treatment of infectious complications required surgical removal of the SQP in just under half of these patients (44%, 8/18). This is in contrast to the literature that has demonstrated antibiotic treatment failure rate ranging from 11% [2] to 14%.[11] This difference may be secondary to the higher incidence of local (i.e., port site or surgical site) infections noted in our group of patients (6/18). Almost all of our patients with infections, salvaged with antibiotics or not, had a documented delay in therapy (17/18).

Limitations of our study

The main limitation of this study is the low event rate. Despite having 614 lines placed over three years, we documented only 18 early post-operative infections. It is therefore difficult to make any strong conclusions with regards to the association between neutropenia and infection. While our multivariable regression model did not find a statistically significant association between neutropenia and infectious complications, the odds ratio was still quite large (2.42). It would be interesting to see how this relationship may change with a higher event rate. Our small event rate also limited our ability to fit multiple variables into our second multivariable regression model due to offer fitting and likely contributed to the wide confidence intervals seen throughout our analyses.

A second limitation of this study is that it is retrospective in nature and therefore has inherent bias built into its design. An example of this was our definition of CLABSI. We chose to accept all infections wherein a pathogen was isolated from a culture drawn through the central line. However, a more restrictive measure would have involved comparing cultures between central and peripheral venous samples and documenting a 5:1 ratio in microbe counts. This would have eliminated the potential for contaminated specimens. Not all patient had peripheral and central blood cultures drawn and therefore this comparison could not be made.

Conclusion and Future directions

The optimal timing of SQP placement in the pediatric oncology patient remains ill-defined. Our results did not show a significant main effect of neutropenia on early post operative infection following SQP placement. Univariable analysis found fever, underlying disease, previous chemotherapy, and hemoglobin were significantly associated with infection, and when these were assessed in the multivariable model, only fever was found to be associated with infection after accounting for the other three variables. Further studies will be required to further assess the relationship between neutropenia and fever on early post-operative wound infections following central line placement in the pediatric oncology patients. Given the low event rate, a multicenter prospective trial or large retrospective database would likely be necessary to further evaluate this relationship.

Table 1. Patient Characteristics by ANC level

	ANC >= 500/mm^3 N = 535	ANC <500/mm^3 N = 79	OR, 95% CI	P Value
Age	109.3 (74.7)	81.0 (58.7)		0.0002[1]
Gender				0.904[2]
Female	43% (202)	44% (33)	F:M	
Male	57% (265)	56% (42)	1.51 (0.72,1.85)	
BMI	23.0 (70.0)	18.2 (5.5)		0.1217[1]
Disease				<0.0001[2]
LL	50% (268)	94% (74)	LL:ST	
ST	50% (267)	6% (5)	13.99 (5.57,35.16)	
Fever				<0.0001[2]
No	95% (510)	78% (62)	Y:N	
Yes	5% (25)	22% (17)	5.59 (2.86,10.94)	
Chemo Prior				0.0359[2]
No	65% (348)	77% (61)	Y:N	
Yes	35% (187)	23% (218)	0.55 (0.32,0.96)	
Previous Catheter				0.0024[2]
No	60% (323)	78% (62)	Y:N	
Yes	40% (212)	22% (17)	0.42 (0.24,0.73)	
Service Placing				0.6885[2]
IR	26% (140)	24% (19)	Surgery:IR	
Surgery	72% (395)	76% (60)	1.12 (0.64,1.94)	
Location Catheter				0.1490[2]
IJ	32% (172)	24% (19)	SCV:IJ	
SCV	68% (363)	76% (60)	1.50 (0.87,2.58)	
Port site				0.7061[2]
Chest	50% (265)	52% (41)	CW:SCL	
Sub clavicular	50% (269)	48% (38)	1.09 (0.68,1.76)	
Hemoglobin	10.97 (2.11)	9.00 (1.32)		<0.0001[1]
Post Op Infection				<0.0001[2]
No	98% (510)	91% (72)	Y:N	
Yes	2% (11)	9% (7)	0.22 (0.08,0.57)	

Continuous variables presented as means and standard deviations. Numbers after percent are frequencies. Tests used [1]TTest; [2] Pearson X^2 test. BMI (Body Mass Index). LL (Leukemia, Lymphoma). ST (Solid Tumor). IR (Interventional Radiology). IJ (Internal Jugular Vein). SCV (Subclavian Vein). CW:SCL (Chest Wall, Subclavicular)

Table 2. Early post operative infectious complications

	N	
Type of infection	18	
Bacteremia		67% (12)
Port Site		22% (4)
Tunnel/track		0% (0)
Bacteremia and port		11% (2)
Organism Isolated	14	
Capnocytopagea		7% (1)
Coag Neg Staph + Candida		7% (1)
Escherichia coli		21% (3)
Moraxella non-liquefaciens		7% (1)
Pseudomonas aeruginosa		7% (1)
Rothia mucilaginosa		7% (1)
Staphylococcus epidermidis		7% (1)
Staphyloccocus aureus		28% (4)
Streptococcus viridans		7% (1)
ANC at time of infection	18	
0		56% (10)
100		11% 92)
300		6% 91)
400		6% 91)
500		6% (1)
600		6% (1)
900		6% (1)
2500		6% (1)
Intervention	18	
Antibiotics		56% (10)
Surgical removal SQP		11% (2)
Antibiotics and surgery		33% (6)
Delay in therapy	18	
Yes		94% (17)
No		6% (1)

Table 3. Association between neutropenia and infection: Assessing confounding

	OR	95% CI	P-value	Percent change
Neutropenia	4.63	1.74-12.33	0.0021	0.0000
BMI adjusted	4.68	1.75-12.48	0.0021	-1.07
Disease adjusted	3.32	1.19-9.27	0.0222	39.63
Previous Catheter adjusted	4.44	1.64-12.00	0.0033	4.28
Fever adjusted	3.06	1.06-8.82	0.0386	1303.03
Chemo Prior adjusted	4.75	1.74-12.96	0.0023	-2.23

Table 4. Association between neutropenia and infection adjusting for fever, and underlying disease

	OR	95% CI	P-value
Neutropenia Y:N	2.42	0.82-7.18	0.1106
Fever Y:N	4.72	1.55-14.37	0.0063
Disease LL:ST	2.33	0.61-8.86	0.2158

LL (Leukemia, Lymphoma). ST (Solid Tumor). Y (Yes). N (No)

Table 5. Univariable Analysis: Predictors of infection

	OR	95% CI	P-value
Fever (Y:N)	7.78	2.76-21.93	0.0001
Disesae (LL:ST)	3.92	1.12-13.69	0.0321
Location Catheter (SCV:IJ)	1.18	0.41-3.36	0.7570
Port Site CW:SCL	1.45	0.54-3.85	0.4588
Chemo Prior Y:N	0.42	0.12-1.48	0.1780
Service Placing Sx:IR	1.23	0.40-3.79	0.7185
Previous Catheter Y:N	0.64	0.22-1.82	0.4003
Preop Infection Y:N	1.11	0.25-4.97	0.8849
BMI	1.00	1.00-1.00	0.6987
Age	1.00	1.00-1.00	0.3795
Gender F:M	1.63	0.63-4.18	0.3124
Glucose	1.00	0.99-1.02	0.5379
Hemoglobin	0.75	0.58-0.96	0.0251
Catheter Size	1.08	0.79-1.50	0.6343

LL(Leukemia, Lymphoma). ST (Solid Tumor). IR (Interventional Radiology). IJ (Internal Jugular Vein). SCV (Subclavian Vein). CW:SCL (Chest Wall, Subclavicular). Y (Yes). N (No)

Table 6. Multivariable Analysis: Predictors of infection

	OR	95% CI	P-value
Disease LL:ST	4.67	2.08-17.81	0.0564
Fever Y:N	6.09	2.08-17.81	0.0010

LL (Leukemia, Lymphoma). ST (Solid Tumor). Y (Yes). N (No).

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INSTITUTIONAL REVIEW BOARD APPROVAL

UNIVERSITY OF MEMPHIS

Institutional Review Board
Office of Sponsored Programs
University of Memphis
315 Admin Bldg
Memphis, TN 38152-3370

Oct 19, 2017

PI Name: Lisa VanHouwelingen
Co-Investigators:
Advisor and/or Co-PI: Vikki Nolan
Submission Type: Initial
Title: Acute Post-Operative Infectious Complications of Subcutaneous Port Placement in Pediatric Oncology Patients: A Comparative Study of Neutropenic and Non-Neutropenic Patients
IRB ID : #PRO-FY2018-60

Expedited Approval: Oct 13, 2017
Expiration: Oct 13, 2018

Approval of this project is given with the following obligations:

1. This IRB approval has an expiration date, an approved renewal must be in effect to continue the project prior to that date. If approval is not obtained, the human consent form(s) and recruiting material(s) are no longer valid and any research activities involving human subjects must stop.

2. When the project is finished or terminated, a completion form must be submitted.

3. No change may be made in the approved protocol without prior board approval.

Thank you,
James P. Whelan, Ph.D.
Institutional Review Board Chair
The University of Memphis.

INSTITUTIONAL REVIEW BOARD APPROVAL

ST JUDE CHILDREN'S RESEARCH HOSPITAL

Institutional Review Board #00000029
FWA00004775

March 8, 2017

Israel Fernandez Pineda, MD
SURGERY

RE: **XPD16-155** - ACUTE POST-OPERATIVE SURGICAL COMPLICATIONS OF SUBCUTANEOUS PORT PLACEMENT IN PEDIATRIC ONCOLOGY PATIENTS: A COMPARATIVE STUDY OF NEUTROPENIC AND NON-NEUTROPENIC PATIENTS

Dear Dr. Fernandez Pineda:

This is to certify that, on 3/8/2017, the
Response dated 3/7/2017 to the 12/9/2016 expedited review of the new research application: XPD16-155 initial protocol dated 10/25/2016, and MRN list,
submitted to the Institutional Review Board for consideration was reviewed by an IRB member using expedited procedures with respect to the adequacy of protecting the rights and welfare of participants, the use of appropriate methods of securing informed consent, the measures to be taken to minimize risk and the degree of risk relative to the potential benefits of the proposed research.

IRB Review Status:
This study is approved for the period of one year under 45CFR46.110(b)(1), Research Category #5, and under children's category 45CFR46.404. The consent and assent requirements are waived under 45CFR46.116(d). Waiver of HIPAA authorization is granted under 164.508 and 164.512(i).

IRB Approval Date: 3/8/2017
IRB Expiration Date: 3/8/2018

For further assistance, please contact the Office of Human Subjects' Protection at 901-595-4357 or email hsp-1@stjude.org.

(Submission Link: Pro00007207)

Reminder of Principal Investigator's Responsibilities:
As previously signed and certified, approval of this research involving human subjects is contingent upon your agreement:

1