The Effect of Dual Policy Interventions on the Rate of Central Venous Catheter Associated Infections in Adult Stem Cell Transplant Patients with Hematological Malignancy in Newfoundland and Labrador

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Abstract

Background:

Central venous catheters (CVCs) have a risk of infectious complications. With a suspected rise in cases in stem cell transplants, Eastern Health implemented two changes to reduce infections in June 2018: (1) earlier CVC insertion and (2) restriction of CVC access to specially trained nurses. The primary outcome was the difference in rate of CVC-associated infections per 1,000 catheter-days. Secondary outcomes included identifying modifiable risk factors to target for future clinical interventions to lower complication rates.

Methods:

This single-centre observational before-and-after study included adult SCT patients with CVCs was divided into the pre- and post-intervention cohorts between 2014-2020. A complete chart review was conducted from the period of first CVC insertion through the endpoint of CVC removal or patient death to identify all incident cases of CVC associated infection, risk factors, cultures and 90-day all-cause mortality.

Results:

The study demonstrated an incidence of catheter-related bloodstream infections (CR-BSI) of 21.3% in the pre-intervention group and 25.0% in the post-intervention group (p=0.681). CR-BSI per 1000 catheter-days was similarly 2.39 and 3.39 (p=0.628). Neither was statistically significant. The study identified a novel risk factor in preceding history of bacteremia (HR 763.1, p=0.039). In

conclusion we were unable to demonstrate a reduction in infectious complications associated with the two interventions.

Key words: Central venous catheter, infectious complication, stem cell transplant, bone marrow transplant, CR-BSI

General Summary

Patients with blood and bone marrow cancers sometimes require stem cell transplants. These transplants require constant access to the patient's blood vessels using a device called a central venous catheter (CVC) which carry a risk of infection.

This study examined whether the restriction of access to these CVCs to trained nurses, as well as early insertion of the devices in the transplant process might reduce the risk of infection.

We found that Eastern Regional Health Authority (Eastern Health) had a lower rate of infection than other centres. However, we did not find that the two interventions in the study were effective in lowering the rate of infection. The study confirmed two known risk factors for infectious complications: the type of device used and the site of insertion. The results also introduced a new risk factor: a previous bacterial infection of the blood. Finally, the study was able to contribute to an existing hypothesis that approximately half of bloodstream infections do not relate to the CVC but instead to breakdown in the gut of these patients due in part to the treatment they receive.

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First I extend my thanks for my mentor in Hematology and the clinician who first approached me with this research opportunity, Dr. David Jones. Your obvious concern for your patients and the operation of a clinically effective stem cell transplant program are clear in your work every day. Thank you for all of the opportunities to learn, grow as a clinician and to build a career in this discipline.

Additionally thank you to Dr. Peter Daley who served as my supervisor for this research project. Your regular feedback throughout helped to shape a project that will have a real impact on patient care and to ensure it has a life beyond this thesis. Also thank you to my co-supervisor, Dr. Kathy Hodgkinson. Your attention to detail and navigating the processes of academia was invaluable to the completion of this work.

I also extend gratitude to the Infection Prevention and Control Committee of Eastern Health and the nurses of 4NA of the Health Sciences Centre and the Ambulatory Treatment Program. Your commitment to patient safety and excellence in clinical care underpins all of the work this thesis examines.

Finally, I wish to extend the biggest thank you to my wife, Jennifer Dunne. Without your commitment and support this thesis and Masters program would never have been possible.

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List of Abbreviations

ANOVA	Analysis of Variance
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
CDC	Centre for Disease Control
CE	Clinical Epidemiologist
CFU	Colony Forming Unit
CHO	Clinical Hematological Oncologist
COVID-19	Coronavirus Disease 2019
CR-BSI	Catheter-Related Blood Stream Infection
CR-TLI	Catheter-Related Tunnelled Line Infection
CVAD	Central Venous Access Device
CVC	Central Venous Catheter
DLBCL	Diffuse Large B-Cell Lymphoma
ICU	Intensive Care Unit
IDS	Infectious Disease Specialist
IDSA	Infectious Disease Society of America
IJ	Internal jugular
MDS	Myelodysplasic syndrome

PICC	Peripherally Inserted Central Catheter
SCT	Stem Cell Transplant
TCPS-2	Tri-Council Policy Statement 2

Chapter 1: Introduction

1.1 Central Venous Catheters

Central venous catheters (CVCs) are a core component of the delivery of chemotherapy and other intravenous therapy in the management of hematological malignancies.[1] These devices support the complex chemotherapy, stem cell transplant and supportive care required to manage advanced malignancies. They provide multiple lumens allowing simultaneous delivery of multiple therapies through a single port. CVCs remain in situ for extended periods of time and reduce the need for repeated venipuncture and provide a convenient access point for blood draws.[2]

CVCs are long thin tubes with multiple lumens which are inserted into a large vein, typically the right internal jugular (IJ) vein in the neck. They are typically placed under sterile conditions by an interventional radiologist or in the operating room by a surgeon or anesthesiologist. Placement involves two incisions, one at the site of the major vein being accessed and the second in the thoracic wall.[3] A tunnel is then created through subcutaneous tissue between the sites allowing the CVC to exit at the latter incision site on the chest wall. The exit site is secured by means of a cuff under the skin.[3]

There are a variety of classes of CVCs with multiple types of catheter within each class. Two varieties used in the SCT program at Eastern Regional Health

Authority (Eastern Health) in Newfoundland and Labrador are Hickman catheters and Permacath catheters. The Hickman catheter is a proprietary medical device developed by Robert O. Hickman in 1979 and features a tissue ingrowth cuff to secure it.[4] Permacath is a proprietary silicon catheter used primarily for short-term dialysis access (Figure 1.1).

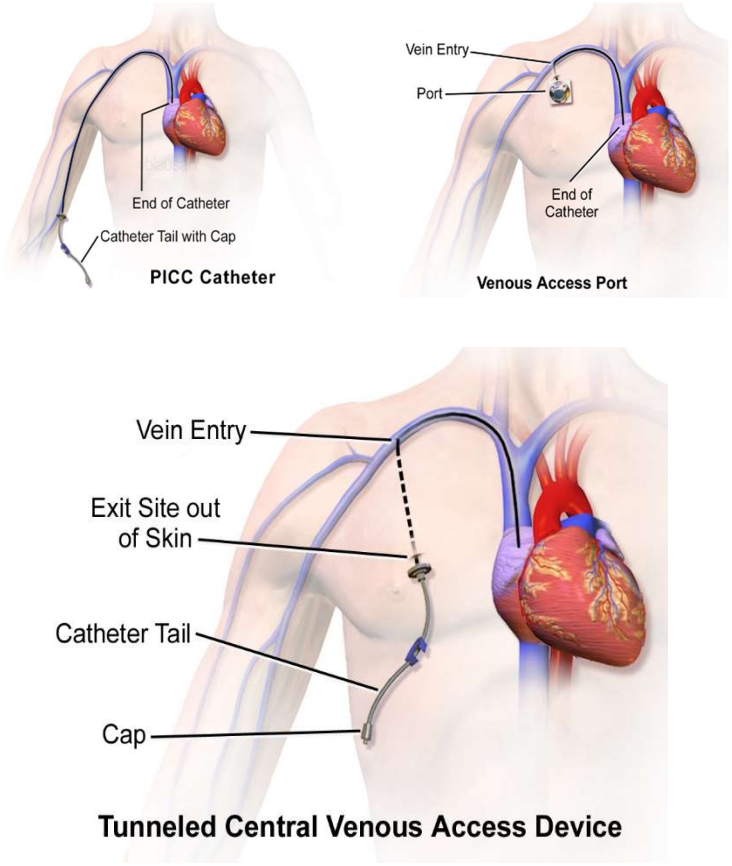

Figure 1.1: Central Venous Access Devices[5,6,7]

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Non-tunneled catheters are fixed in place directly at the site of insertion, while tunneled catheters pass the catheter under the skin.[8] Peripherally inserted central catheters (PICCs) are inserted through a vein in the arm and advanced

into a large central vein.[8] These three classes leave a portion of the catheter exposed above the skin. An implanted port is a further class of device that buries the entirety of the apparatus under the skin (Figure 1.1).[8] The devices utilized in the patient population for this study includes Hickman catheters, Permacath catheters and PICC lines.

1.2 Infectious Complications

CVCs carry a significant rate of complications including three types of infectious complication

i) catheter-related bloodstream infections (CR-BSI),

ii) catheter-related tunneled-line infections (CR-TLI), and

iii) exit-site infections.

These are significant complications with a reported mortality rate for CR-BSI in cancer patients of 12 to 40% per episode.[9] Beyond the significant risk of mortality, infectious complications can impede care and lead to morbidity. The requirement to remove the CVC due to infection can delay treatment of the underlying malignancy and exposes the patient to the risks of reinsertion in a patient often at increased risk of bleeding due to thrombocytopenia.[8]

The use of CVCs in other settings - particularly in the intensive care unit and solid tumor malignancies - has been robustly studied with meaningful reductions in complications such as CR-BSI.[10,11] In the ICU setting the rate of infectious complications ranges from 3.8-11.3 events per 1000 catheter-day[10,11] and in all-

cancer populations the rate ranges from 0.02 to 3.2.[14,15] The rate of CVC infection amongst SCT patients will be presented in the literature review section.

CVC infection may require the removal of the CVC, which is a negative outcome. Ideally, the CVC will remain infection-free for the duration of the SCT period and be removed when no longer needed rather than be removed prematurely due to infection.

1.3 SCT & Infectious Risk

Hematopoietic SCT is the transplantation of pluripotent hematopoietic stem cells from the bone marrow, peripheral blood or umbilical cord blood.[16] It is a procedure with significant risks, typically reserved for the treatment of cancers of the blood or bone marrow.[16] Autologous SCT use stem cells are sourced from the patient, while allogeneic SCT use stem cells provided by donors.[17] Eastern Health performs only autologous SCT locally, while allogeneic SCT are conducted at partner facilities in Eastern Canada. Hematological malignancies undergoing SCT at Eastern Health between 2013-2020 are detailed in Table 1.1. Evidence regarding the incidence and specific risk factors for CR-BSI in this subset of patients has begun to emerge in the last 15 years, though studies have utilized inconsistent methodologies and produced variable results particularly regarding risk factor identification.

Table 1.1: Indications for Autologous Stem Cell Transplant

Eastern Health Hematopoietic Stem Cell Transplant Program
Hematologic Malignancy
Multiple Myeloma
Mantle Cell Lymphoma
Grey Zone Lymphoma
Diffuse Large B-Cell Lymphoma
B-cell Non-Hodgkins Lymphoma
Hodgkins Lymphoma
T-Cell Lymphoma
Primary CNS Lymphoma
Anaplastic Large Cell Lymphoma

Hematological malignancy has been established as an independent risk factor for the development of CR-BSI.[18] These patients are at an increased risk of acquiring infection due to immunocompromise inherent in hematological malignancy, extended neutropenia induced through intensive chemotherapy, and increased requirement for blood products.[19,20] Patients receiving SCT are a subset of hematological malignancy patients who have a further immunocompromise due to therapy given to establish the transplant.[21]

1.4 Study Purpose

The Hematological Oncology service at Eastern Health in St. John's, Newfoundland and Labrador became concerned with what they believed to be an increased rate of infectious complications in SCT patients with a CVC, beginning in mid-2017.

In June 2018 the Hematological Oncology service, working in conjunction with the Eastern Health Infection Prevention and Control Committee, implemented two interventions targeting a reduction in these rates. The first was a change in the timing of CVC insertion in SCT patients to minimize immunosuppression at the time of insertion. The second change was to nursing policy, limiting access to CVCs to trained in-patient nurses. These interventions are further delineated below.

The purpose of this pre- and post-intervention cohort study is to investigate the baseline incidence, associated risk factors, causative organisms and mortality for CVC associated infections for hematological malignancy patients receiving autologous SCTs in Newfoundland and Labrador between January 2014 and June 2018. The study examined the post-intervention cohort to determine the effect of these interventions on the rate of CVC infectious complications in patients between June 2018 and March 2020.

Intervention #1: Altering the Timing of CVC Insertion

A single small trial of timing of CVC placement in patients with acute leukemia suggested that delayed insertion during the treatment period may be associated with increased rates of infection.[22] Data was not available on timing of insertion and infectious risk in the SCT population. Previously at Eastern Health CVCs were inserted on Day 4-5 in the collection phase of transplant after the delivery of cytotoxic chemotherapy and immunosuppressive steroids. In the revised timing,

the CVC is inserted on Day -2 or -1 prior to the delivery of immunosuppressive therapy (Figure 1.2). The clinical team hypothesized that inserting the CVC while the patient's immune system is still relatively intact would reduce risk of infection.

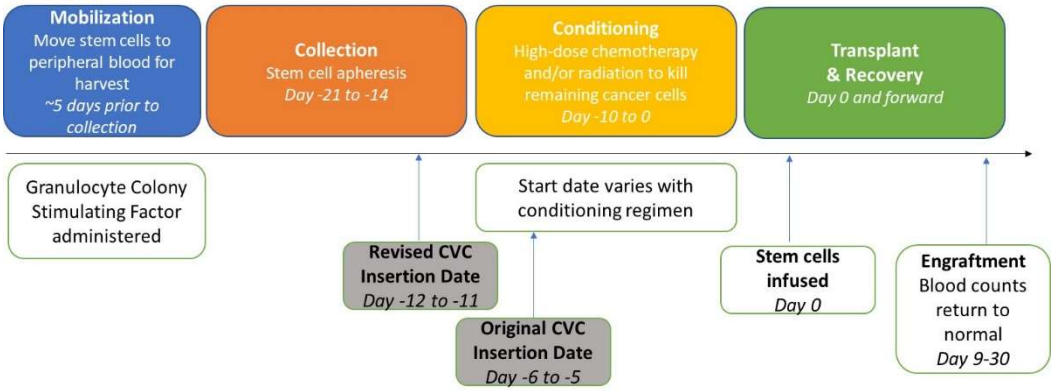

Figure 1.2 Transplant Timelines with Modified CVC Insertion Timing

Intervention #2: Nursing Policy Change

It was also identified that CVCs were being accessed by community nursing staff with variable levels of CVC training and experience during the interval between collection and transplant when the patient was seen as an outpatient. Adherence to Central Venous Access Device (CVAD) policy was unknown in this population. As such, the working group implemented an intervention of providing a clinical educator to review the existing CVAD policy with inpatient nurses and to restrict access to CVCs to inpatient and ambulatory treatment clinic nurses.

1.5 Research Questions

General:

To determine the effect of two interventions on the incidence, associated risk factors, causative organisms and all-cause mortality for CVC associated infections among hematological malignancy patients receiving SCT in Newfoundland and Labrador.

Specific:

Primary

1. What is the effect on incidence per 1000 catheter days of CR-BSI, CR-TLI, exit-site infections and total CVC associated infectious complications in adult hematological malignancy patients receiving SCT with a CVC placed in Newfoundland and Labrador between January 2014 and June 2020?

Secondary:

1. What is the baseline incidence and incidence rate per 1000 catheter days of CR-BSI, CR-TLI, exit-site infections and total CVC associated infections in adult hematological malignancy patients receiving SCT with a CVC placed in Newfoundland and Labrador between January 2014 and June 2018?

2. What are the associated risk factors of CVC associated infections in adult hematological malignancy patients receiving SCT with a CVC placed in Newfoundland and Labrador between January 2014 and June 2020?

3. What is the all-cause inpatient mortality rate for adult hematological malignancy patient receiving once a diagnosis of CVC associated infection is

made for patients with a CVC placed in Newfoundland and Labrador between January 2014 and June 2020?

4. Do hematological malignancy patients with autologous SCT and CR-BSI experience positive cultures for gut- associated bacteria (enteric Gram negative bacteria, *streptococcus viridans*)?

1.6 Hypotheses

Primary Hypotheses:

1. Incidence Rate per 1000 catheter days

- H_o=0 There is **no** difference in incidence rate per 1000 catheter days of total CVC associated infectious complications in adult hematological malignancy patients.
- H_a≠0 There is **a** difference in incidence rate per 1000 catheter days of total CVC associated infectious complications in adult hematological malignancy patients.

Secondary Hypotheses:

1. Mortality

- H_o=0 SCT patients with CVC associated infection **do not** have higher risk of all-cause mortality than those without infectious complication.
- H_a≠0 SCT patients with CVC associated infection **do** have higher risk of all-cause mortality than those without infectious complication.

Chapter 2: Review of Literature

2.1 Data Sources & Search Protocol

The literature review was conducted of PubMed, EmBASE and Cochrane Library utilizing the MeSH terms (Hematologic* malignancy OR hematologic malignancies); AND (catheterization, central venous OR central venous catheterization) AND infection AND sepsis AND incidence AND risk factor*. The search strategy filtered results for human studies in English for participants 19+ years of age. No time limit was placed on the search. Studies included in the search were systematic reviews, meta-analyses, randomized control trials, prospective and retrospective cohort studies and case series. References for relevant papers were reviewed to identify any additional studies of interest.

2.2 Background Information

The literature review identified five cohort studies that examined the epidemiology of CVC infectious complications in adult hematological malignancy patients.[20,21,23-25] There was a high degree of variability in the study designs. The study designs were mixed in terms of patient populations with some studies including only SCT patients[21], some excluding SCT patients[20], and others examining all hematological malignancy patients.[21,23-25] These subgroups are highly variable in the characteristic of their underlying malignancy, the degree of immunosuppression related to SCT preparation and maintenance, and the chemotherapy delivered. The studies also had a mix of primary outcomes with

most studies looking exclusively at CR-BSI.[21,23,24] While one study examined all CVC infectious complications, it did not provide a separate incidence for each subtype.[25] Worth et al examined both CR-BSI and exit-site infections but did not report on CR-TLI.[23] The overall infectious complication incidence in these studies ranged from 24.7-31.3% per CVC line placed, significantly higher than rates quoted for non-hematological malignancy CVC patients.[12-15] Only three studies reported incidence rate per 1000 catheter days. The range for these results combined was 5.2-7.6/1000 indwelling days (Table 2.1).[20,23,24]

Table 2.1: CVC Infectious Complications in Hematological Malignancy Literature Review Summary

Study	Design	Population	Outcome	Incidence	Incidence Rate Per Catheter Days
Worth *et al.*	Prospective Cohort	Adult hematological malignancy +/- Autologous SCT	CR-BSI	31.1%	7.5 (4.45-11.86)
			Exit Site Infections	1.9%	0.83 (0.10-3.01)
Lukenbill *et al.*	Retrospective Cohort	Adult AML + MDS with Allogeneic SCT	CR-BSI	32%	Not reported
Dix *et al.*	Prospective Cohort	Adult hematological malignancy	CR-BSI	24.7%	7.6
Cortellezzi *et al.*	Retrospective Cohort	Adult hematological malignancy	CR-BSI	25.8%	5.2
Sariosmanoglu *et al.*	Prospective Cohort	Adult hematological malignancy	All CVC Infections	26.6%	Not reported

Four studies examined risk factors associated with CVC infectious complications among adults with hematological malignancy.[20,21,23,27] All these studies looked at associations with CR-BSI only. The reported risk factors are often in conflict and no study replicated a single risk factor identified in another study. In some instances, risk factors that would seem to be clinically relevant were not found to have an association (neutropenia, length for time in-dwelling). Others like Girard

et al.'s finding of lymphoma as an associated risk factor are out of step with all previous studies (Table 2.2).[12]

Table 2.2: Risk Factors Associated with CR-BSI in Hematological Malignancy				
Risk Factors	**Worth *et al.***	**Lukenbill *et al.***	**Girard *et al.***	**Dix *et al.***
AML	OR 0.144 (0.021-0.97, p=0.046)			
History of previous fungal infection	OR 22.82 (1.339-388.953, p=0.031)			
Cord blood transplant		HR 14.19 (5.41-37.18, p=0.002)		
High Stem Cell Transplant Co-Morbidity Index		HR 4.68 (1.81-12.13, p=0.002)		
Groshong catheter			RR 5.75 (2.58-12.77, p<0.001)	
Lymphoma			RR 3.19 (1.05-9.68, p=0.041)	
Erythropoietin			RR 2.88 (1.31-8.48, p=0.009)	
Number of Treatments			RR 0.68 (0.46-0.99, p=0.047)	
Acute Lymphocytic Leukemia				OR 5.0 (1.32-18.92, p=0.02)
Subclavian vein site				OR 0.11 (0.003-0.52, p=0.004)

Helpfully, the studies highlight some under-investigated markers of immunosuppression which this study will include: corticosteroid burden and erythropoietin administration. Corticosteroids had been previously identified as a risk factor for infection when used for treatment of graft-versus-host disease in allogeneic SCT patients, however data was not available assessing it as a baseline risk factor in all SCT patients.[28] The study by Girard *et al.* is the only

available data on erythropoietin use and infectious complications in the literature for the SCT population.

Chapter 3: Methods

3.1 Research Setting

The study was conducted at the Health Science Centre in St. John's, Newfoundland and Labrador. This is the single SCT centre for the province and provides autologous SCT. Patients requiring allogeneic SCT are referred out of province for completion of their procedures. Transplant patients are not discharged with CVCs in place, meaning that all data relevant to the study was contained in the patient chart for a single admission to hospital.

3.2 Data Sources

Study participants were identified through the Newfoundland and Labrador Stem Cell Transplant and Hematological Malignancy Patient Registry as detailed above. Data was generated from patient charts accessed through the Eastern Health Meditech system, or where paper records were required through the Eastern Health Health Information Services and Informatics department.

3.3 Study Design

Similar to most studies examining infectious complications in CVCs in hematological malignancy this study is a single-centre descriptive cohort study. The group of interest in this study is adult hematologic malignancy patients undergoing SCTs. The study compares the population prior to two policy interventions targeting a reduction in rates of CVC associated infectious complications (Figure 3.1). The study was restricted to inpatients given the wide

disparity in infectious complications in outpatient hematology patients with central lines reflective of lower underlying immunosuppression from both disease and treatment characteristics.[26]

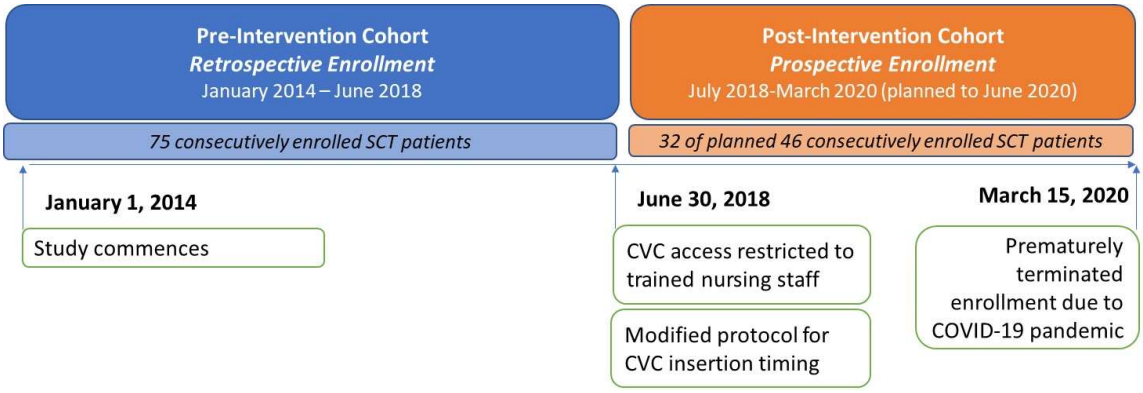

Figure 2.1 Study Timeline

All consecutive SCT patients who underwent CVC placement for inpatient treatment between January 2014 and June 2020 were included in the study. The group of interest represented approximately 25 autologous SCT patients per year with an increasing annual rate of SCT throughout the study period. These patients are registered in the Newfoundland and Labrador Stem Cell Transplant and Hematological Malignancy Patient Registry maintained by the Hematological Oncology group at Eastern Health and were identified by querying the registry for new patients in the timeframe of the study. Only patients with elective or semi-elective CVC placement under radiologic guidance were included in this study. Emergently placed lines are placed in uncontrolled conditions in comparison to planned line placements performed by interventional radiology. Emergently placed lines occur when patients are unwell, may occur in environments such as

the emergency department or intensive care unit, and are not typically performed by an interventional radiologist. Infectious risks are higher during these procedures and as such lines placed emergently or in the intensive care unit (ICU) setting are excluded.

3.4 Study Procedure

The principal investigator reviewed the patients identified through the patient registry for inclusion and exclusion criteria as described below. Patients meeting the criteria underwent a chart review by the principal investigator. Any data from the chart review that was clinically ambiguous regarding an infectious outcome as defined in the- study was anonymized then reviewed by the Infectious Disease Specialist and the Hematologic Oncologist. A decision was made by interpreting the available clinical data, applying the relevant study definition and classified as either a type of infectious complications, as a non-event, or as unable to evaluate. A sensitivity analysis was planned to evaluate data with cases deemed unable to evaluate as infectious complications and as non-events however no such event occurred in the chart review.

Patients were followed until the CVC was removed either: i) at the conclusion of treatment, ii) due to complication, or iii) death. Ninety-day mortality was documented for each patient from the time of line removal. For patients who had a CVC replaced, the new CVC was included as a discrete CVC for the purposes of infectious complication incidence, risk factors and microbiology cultures

calculations. For mortality, the denominator utilized is total patients rather than total lines placed.

3.5 Study Participants

P - Patients	Adult hematological malignancy patients over the age of 18 receiving a SCT in Newfoundland and Labrador, Canada between January 2014 and June 2018	
	Inclusion Criteria	**Exclusion Criteria**
	Any hematological malignancy requiring SCT, including myelodysplastic syndrome	Known infection at time of CVC insertion
	Any type of central venous catheter	CVC inserted in ICU setting
	Elective or semi-elective CVC insertion	Peripherally-inserted central catheter
		Treated in outpatient setting
I - Intervention (Exposure)	1. Earlier insertion of CVC 2. Nursing policy restricting CVC access to inpatient nurses trained in infection control procedures	
C - Control (Comparison Group)	Adult hematological malignancy patients over the age of 18 receiving a SCT between July 2018 and June 2020	
O - Outcomes	**Primary:** 1. New diagnosis of catheter-related infectious complication (exit-site, tunnel infection CR-BSI)	
	Secondary: 1. All-cause mortality with follow up to discharge	
T - Time	Admissions between January 1, 2014 and June 2020	

Table 3.1: PICO Question

3.6 Outcome Definitions

3.6.1 CR-BSI

There is not currently a consensus regarding the surveillance definition of CVC infectious complications in the literature - not only for hematologic malignancy patients, but in other settings as well.[29] Further, clinical definitions of CVC associated infection differ from surveillance definitions. Clinically, other sources of infection are sought by patient examination, laboratory evaluation and chart

review. If an alternate source for infection cannot be identified, then it is often attributed to the CVC without definitive evidence. This is particularly the case for bacteremia without source in the surveillance definitions. If the CVC is pulled a culture of the catheter tip is performed to confirm CVC implication in the infection.[29] In this population the practice is often to attempt to preserve the CVC in situ through the treatment of underlying infection. This makes it impossible to fulfill the "definitive" criteria in the surveillance definitions for infectious complications, which include culture results from the CVC tip after removal.

A summary of the surveillance definitions utilized for CR-BSI in the literature is below, further complicated by the 2013 introduction of the modified CDC definition which excludes bacteria likely of a gastrointestinal source in hematology patients.[30]

The surveillance definitions from the United States are stringent and offer the best evidence for proving a CVC infectious complication. However, the local microbiology laboratory does not report culture results quantitatively nor include time to growth, therefore these definitions cannot be utilized in this chart review. Therefore, the Public Health Agency of Canada definitions will be used in this study, which is consistent with the existing Infection Control definition used at Eastern Health (Table 3.2).

Table 3.2: CR-BSI Surveillance Definitions	
Organization	**Defintion**
CDC[31]	Clinical manifestations of infection
	At least 1 positive blood culture from a peripheral vein with either positive semiquantitative (>15 CFU/catheter segment) or quantitative (>10^3 CFU/catheter segment) from a catheter tip with the same species and antibiogram
	OR
	Simultaneous quantitative cultures of blood samples (catheter v peripheral) with a ratio of >3:1
	OR
	Differential period to culture positivity for catheter v peripheral of 2 hours
	OR
	Positive blood culture + symptoms of BSI AND no identifiable source
IDSA[32]	Positive peripheral blood culture + symptoms of BSI AND no other identifiable source
	AND one of the following
	At least 1 positive blood culture from a peripheral vein with either positive semiquantitative (>15 CFU/catheter segment) or quantitative (>103 CFU/catheter segment) from a catheter tip with the same species and antibiogram
	Simultaneous quantitative cultures of blood samples (catheter v peripheral) with a ratio of >5:1
	Differential period to culture positivity for catheter v peripheral of 2 hours
Public Health Agency of Canada[33]	**Definite:** Single positive blood culture and positive culture of exit site or tunnel exudate with identical organism
	OR
	Single positive blood culture and positive culture from catheter tip with identical organism or >10-fold colony count difference in tip v. peripheral blood
	Probable: >1 positive blood culture with no evidence of source other than CVC
	OR
	Single positive blood culture for *S.aureus* or Candida species with no other source

Table 3.2: Surveillance Definitions of CR-BSI (CDC - Centre for Disease Control, CFU - Colony Forming Unit, IDSA - Infectious Disease Society of America, BSI - Blood Stream Infection)

3.6.2 Exit Site Infections

Exit-site infections are complications that occur at the level of the skin where a device exits the patient. This study will follow the CDC definition of erythema or induration within two centimeters of the catheter exit site in the absence of concurrent BSI and without purulence.[30]

3.6.3 CR-TLI

Tunnel infections are complications which occur in the subcutaneous tissue where the device travels under the patient's skin. This study again employs the CDC definition of tenderness, erythema or site induration greater than two centimeters from the catheter site along the subcutaneous tract of a tunneled catheter, in the absence of concomitant BSI.[30]

3.7 Randomization and Blinding

In the context of a retrospective study, there is no randomization of study participants to exposures. However patient demographics were analyzed to ensure the group of interest and comparison groups are sufficiently similar to allow for statistical comparison.

Considering the nature of chart reviews with clinical data rife with personal identifiers it will not be possible to blind the research assistant in the process of data collection. Data was anonymized as it was entered into the database. Upon completion of the data collection phase the groups, risk factors and microbiology culture results were blinded through use of randomly generated labels. The principal investigator maintained a key in an encrypted, password protected file for unmasking once data analysis is complete.

3.8 Research Team

Given the scope of this study a multidisciplinary team has been assembled. All members completed the Tri-Council Policy Statement 2 (TCPS-2) Core training module prior to initiation of the study.

Core Team:

The **Principal Investigator (PI)** has ultimate responsibility for the conduct of the study. The PI obtained approval from the Health Ethics Research Board. He was be responsible for acquiring access to patient charts, for implementing study protocols for interpretation of clinical data, data management, data analysis and for dissemination of study results. The author served in this capacity for this study.

A **Clinical Hematological Oncologist (CHO)** is responsible for coordinating access to the Newfoundland and Labrador Stem Cell Transplant and Hematological Malignancy Patient Registry to identify patients treated at the Health Science Centre. The CHO was responsible to acquire informed consent when not established in the course of treatment. The CHO served in conjunction with the Infectious Disease Specialist representative to evaluate and adjudicate clinical data from patient charts to match study outcome definitions in accordance with study protocols. Dr. David Jones served as the CHO for the duration of this study.

An **Infectious Disease Specialist (IDS)** from the Eastern Health Infectious Disease department assisted in the development of study definitions for CR-BSI and CR-TLI. The IDS was responsible to adjudicate any ambiguous clinical data with the CHO as described above. The IDS assisted in interpretation of culture results from the microbiology laboratory to ensure that contaminants are not included in study results. Dr. Peter Daley served in the capacity of IDS for the duration of this study.

A **Clinical Epidemiologist (CE)** acted as the primary advisor on study design particularly in establishing protocols for data interpretation and establishing clear outcome definitions. Dr. Kathy Hodgkinson served in the capacity of CE for the duration of this study.

3.9 Statistical Analysis

3.9.1 Data Analysis

Descriptive analysis was conducted to calculate incidence and incidence rate per 1000 catheter days for exit-site infections, tunneled-line infections and CR-BSI, then in aggregate for all infectious complications. The denominator for incidence is total CVC placed, and for incidence rate is total in-dwelling days.

Univariate analysis was conducted utilizing the t-test for continuous variables and Chi-squared test for categorical variables to identify risk factors. Multivariate analysis was conducted utilizing binary logistic regression with an entry criterion for Odds Ratios (OR) of $p \leq 0.20$ with reverse stepwise removal of insignificant

variables. A p-value of <0.05 was considered an indication of statistical significance. Confidence intervals of 95% were calculated. All statistical tests were two-sided. Risk factors assessed in the study are below (Table 3.3).

Days to infectious complication was calculated using the Wilcoxon rank-sum test. An analysis of catheter survival (catheter remains in-dwelling) was performed using a Kaplan-Meier curve for the study population as a whole and for patients who experienced an infectious complication. All-cause 90-day mortality was planned to be calculated using the Kaplan-Meier curve, however as only a single event occurred in the study period there is not sufficient data for reliable analysis. Risk factor analysis as described above was planned to be re-calculated for all-cause 90-day mortality, however this too did not proceed due to too few events in the study period.

All analysis was conducted using IBM SPSS Statistics software Version 26.0.

Table 3.3: Risk Factors to be Assessed for CVC Infectious Complications in Hematological Malignancy			
Risk Factors	**Categorical**	**Continuous**	**Previously Identified Risk Factor**
Patient Factors			
Age		x	
Malignancy Diagnosis	x		x
Transplant Status	x		
History of previous bacteremia	x		
History of previous fungal infection	x		x
HLA match v. mismatch	x		
Immunosuppression			
Chemotherapy type	x		
Number of prior chemotherapy regimens		x	
Corticosteroid burden last 90 days		x	
Erythropoietin use	x		x
Days until PMN>500µL		x	
CVC Factors			
Central line type	x		x
Insertion site	x		x
Antibiotic prophylaxis	x		
Training level of Radiologist (Resident/Staff)	x		
Day of week of insertion	x		
Days in situ		x	
Thrombotic complication	x		

3.9.2 Sample Size

Existing studies in the literature are all cohort studies without comparison groups, and as such do not provide sample size calculations. A power analysis utilized below estimates the sample size required to test the difference in incidence of catheter-related infectious complications before and after the implemented interventions. The level of significance for this study is 5% or $\alpha = 0.05$. The power is 90% or $\beta = 0.10$. An expected effect size of 30% in incidence rate per 1000 catheter days comparing the pre- and post-intervention cohorts was determined to be clinically relevant in this population. The clinically estimated incidence rate based on observation is approximately twice the rate at other centres. As noted

previously, the incidence of catheter-related infection in SCT patients is 32% per CVC placed thus for this population we will use an event rate of 64%. The standard deviation of incidence rate per 1000 catheter days is 0.6.[17,18,20,24]

$$n = 2(Z_{\alpha} + Z_{1-\beta})^2\sigma^2/\Delta^2 = (2(1.96+1.2816)^2(0.12)^2/(0.3)^2 = 84.1$$

The calculated study sample size is 84.1 patients. Given the study design and noting that all patients enrolled are inpatients for the duration of their treatment and have their CVCs removed prior to discharge, loss-to-follow-up should be minimal in this study. Estimating a 10% loss of follow up, a total of 92 samples will be required.

Subsequent to the completion of this power calculation the study committee reviewed the size of the overall population. Given the limited number of patient in the pre-intervention period spread over a significant period of time, and the possibility that the rise in infectious complications were clustered within the 2017-2018 timeframe as suspected based on clinical observations, a decision was made to include all 94 patients in the pre-intervention time period to allow for a more robust cohort and strengthen the certainty of any effects detected. The power calculation was utilized to determine the number of patients in the post-intervention period would be required to detect the effect as described above and to determine when enrollment was complete.

3.9.3 Patient Enrollment & COVID-19

Patient enrollment proceeded as planned for the pre-intervention group as all patients had completed treatment prior to the initiation of data collection. Patients in the post-intervention group were enrolled consecutively as SCTs were completed. This continued until the end of February 2020. In March 2020 the Eastern Health SCT program was suspended given the infectious risk to patients related to the COVID-19 (Coronavirus disease 2019) global pandemic.

In light of this complication the supervisory committee for this thesis met and agreed to suspend data collection. At that point 32 patients had been enrolled in the post-intervention group, or 69.6% of the planned enrollment to meet power calculations. While acknowledging that cessation of data collection at this point would result in an underpowered study, the committee felt it best to proceed with data analysis to deliver some preliminary conclusions given that a resumption timeframe was not yet determined for the SCT program.

Finally, the principal investigator has arranged for data collection to continue with the resumption of the SCT program through a new principal investigator. This will allow a fully powered exploration of the findings in due course.

Chapter 4: Results

4.1 Patient Characteristics

In the pre-intervention period between January 2014 - June 2018 95 charts were included in the study for review. Of those 95 charts there were 94 individuals planned for autologous stem cell transplantation. Seventy-five (75) patients were included in the pre-intervention cohort. Of the 19 exclusions there was one (1) duplicate record, one (1) SCT for a non-hematologic malignancy, and eight (8) patients who underwent stem cell collection only and did not proceed to transplant. In 2014 there was a period of time when autologous transplants were not conducted locally, and patients were transferred out of province for transplant. Nine (9) patients were excluded from this study who underwent out-of-province SCT during this period (Figure 4.1).

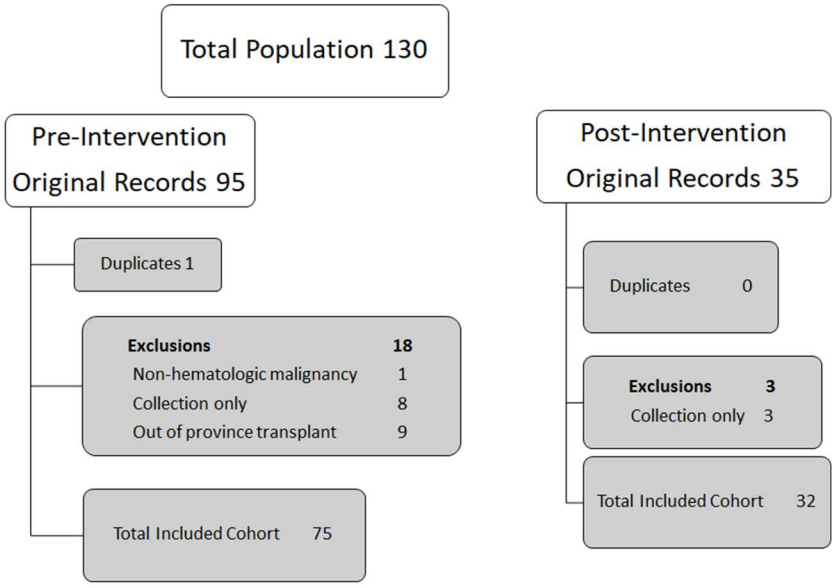

Figure 4.1: Study Population Inclusion and Exclusions

The post-intervention period spanned from July 2018 - March 2020 when the SCT program was suspended due to the COVID-19 global pandemic. During this period charts from 35 consecutive planned SCTs were reviewed. Three (3) patients were excluded from this cohort as they only underwent stem cell collection and did not proceed to transplant.

The pre- and post-intervention groups demonstrated some differences in baseline characteristics. As consecutively enrolled patients representing the entire population for each cohort these differences cannot be explained by randomization. In terms of patient characteristics there were more males in the post-intervention group (71.9% versus 55.8%, p=0.11), they had less myeloma

(53.1% versus 61%, p=0.459) and more diffuse large B-cell lymphoma (DLBCL) (25% versus 15.6%), had less history of bacteremia (3.1% versus 16%, p=0.002) and less history of radiation therapy (6.3% versus 19.5%, p=0.038) (Table 4.1).

In terms of CVC characteristics, the post-intervention group had less antibiotic prophylaxis prior to line placement (0% versus 16.9%, p=0.013), less use of heparin-impregnated CVCs (25% versus 45.5%, p=0.038) and fewer days indwelling (78.73 versus 89.33, p=0.595). Both populations were approximately equivalent in the distribution of types of CVC, number of lines of chemotherapy, CVC insertion site and level of training of radiologist.

Table 4.1: Demographic and Baseline Characteristics

	Pre-Intervention		Post-Intervention		*P* value
Number of Subjects	77		32		
Gender (Male)	43	(55.8)	23	(71.9)	0.11
Mean Age	57.5		56.1		0.59
Malignancy					0.459
Multiple Myeloma	47	(61.0)	17	(53.1)	
Mantle Cell Lymphoma	3	(3.9)	2	(6.3)	
DLBCL	12	(15.6)	8	(25)	
Hodgkins Lymphoma	9	(11.7)	2	(6.3)	
Follicular Lymphoma	2	(2.6)			
Other	4	(5.2)	3	(9.3)	
Transplant Status					
Previous SCT	5	(6.5)	0	(0)	0.24
Transplant Type					
Autologous	77	(100)	32	(100)	
History of Bacteremia	16	(20.8)	1	(3.1)	0.002
History of Fungemia	1	(1.3)	0	(0)	0.32
History of Radiotherapy	15	(19.5)	2	(6.3)	0.038
Lines of Chemotherapy					0.947
1	35	(45.5)	14	(43.8)	
2	29	(37.7)	14	(43.8)	
3	9	(11.7)	3	(9.4)	
4	3	(3.9)	1	(3.1)	
Erythropoietin Use	3	(3.9)	1	(3.1)	0.841
Type of CVC					0.714
PermaCath	60	(77.9)	24	(75.0)	
Hickmann	14	(18.2)	8	(25.0)	
Insertion Site					0.715
Right IJ	71	(92.2)	31	(96.9)	
Left IJ	4	(5.2)	1	(3.1)	
Other	1	(1.3)			
Mean Days CVC In Situ	89.33		78.73		0.595
Antibiotic Prophylaxis	13	(16.9)	0	(0.0)	0.013
Heparin Impregnated CVC	35	(45.5)	8	(25.0)	0.038
Radiologist Level of Training					
Attending	67	(87.0)	27	(84.4)	0.597
Resident	9	(11.7)	5	(15.6)	0.617
Line Replacement Required	9	(11.7)	2	(6.3)	0.714
Thrombotic Complication	6	(7.8)	3	(9.4)	0.795

DLBCL Diffuse Large B-Cell Lymphoma; IJ Internal Jugular;
CVC Central Venous Catheter; SCT Stem Cell Transplant

4.2 Infectious Complication Incidence and Incidence Rates

4.2.1 Incidence Rate

The incidence per 1000 catheter days of infectious complications under the CDC and Public Health Agency of Canada definitions outlined above were compared between the pre- and post-intervention groups. No statistically significant difference was detected in the total incidence rate of infections per 1000 catheter days, or for any of the subtypes of infectious complications. While total infections per 1000 catheter days showed a non-significant improvement from 6.87 to 5.5 ($p=0.763$), this was derived entirely from exit site infections which carry the lowest clinical impact. CR-BSI and CR-TLI showed non-significant increases in incidence rate per 1000 catheter days.

4.2.2 Incidence

No statistically significant difference was detected in the total incidence of infectious complications or any of the sub-definitions between the groups.

The incidence of total infectious complications in the pre-intervention group was 46 cases (59.7%), while in the post-intervention group it was 13 cases (59.4%). The incidence of total CR-BSI in the pre-intervention group was 16 (21.3%), in the post-intervention group there were 8 incident cases (25.0%).

Exit site infection incidence trended toward a statistically significant reduction, with 16.9% in the pre-intervention group and 6.3% in the post-intervention group (p=0.07) (Table 4.2).

Table 4.2: Incidence and Incidence Rate of Infectious Complications

		Pre-Intervention		Post-Intervention		Hazard Ratio	95% CI	*p-value*
Total Infectious Complications								
	Incident Cases	46	(59.7)	13	(59.4)			*0.737*
	Incidence Per 1000 Catheter Days	6.87		5.5		1.106	(0.575, 2.127)	*0.763*
CR-BSI								
Probable								
	Incident Cases	14	(18.2)	7	(21.9)			*0.714*
	Incidence Per 1000 Catheter Days	2.08		2.96		1.233	(0.498, 3.056)	*0.651*
Definite								
	Incident Cases	2	(2.6)	1	(3.1)			*0.9*
	Incidence Per 1000 Catheter Days	0.3		0.42		1.233	(0.112, 13.601)	*0.864*
Total								
	Incident Cases	16	(21.3)	8	(25.0)			*0.681*
	Incidence Per 1000 Catheter Days	2.39		3.39		1.233	(0.538,2.882)	*0.628*
CR-TLI								
	Incident Cases	7	(9.1)	4	(12.5)			*0.645*
	Incidence Per 1000 Catheter Days	1.04		1.69		1.41	(0.413,4.815)	*0.584*
Exit Site Infections								
	Incident Cases	13	(16.9)	2	(6.3)			*0.077*
	Incidence Per 1000 Catheter Days	1.94		0.85		0.379	(0.086, 1.682)	*0.202*

CR-BSI Catheter-Related Blood Stream Infection; CR-TLI Catheter-Related Tunnelled Line Infection

4.2.3 Post-Hoc Review of Incidence and Incidence Rates

In reviewing the data, the failure to identify a difference in incidence and incidence rate in CVC-associated infectious complications did not seem consistent with what was believed to be an observed increase in this population amongst clinicians. It was proposed that the increase may have been limited to a shorter interval than total pre-intervention period spanning from mid-2017 to June of 2018 when these interventions were put in place. The original pre-intervention cohort timeframe was selected to ensure a large enough population to satisfy the power calculations and in light of the overall small population size. A post-hoc

Poisson analysis was conducted comparing these periods (January 2014-June 2017, July 2017-June 2018, July 2018-March 2020) (Figure 4.2).

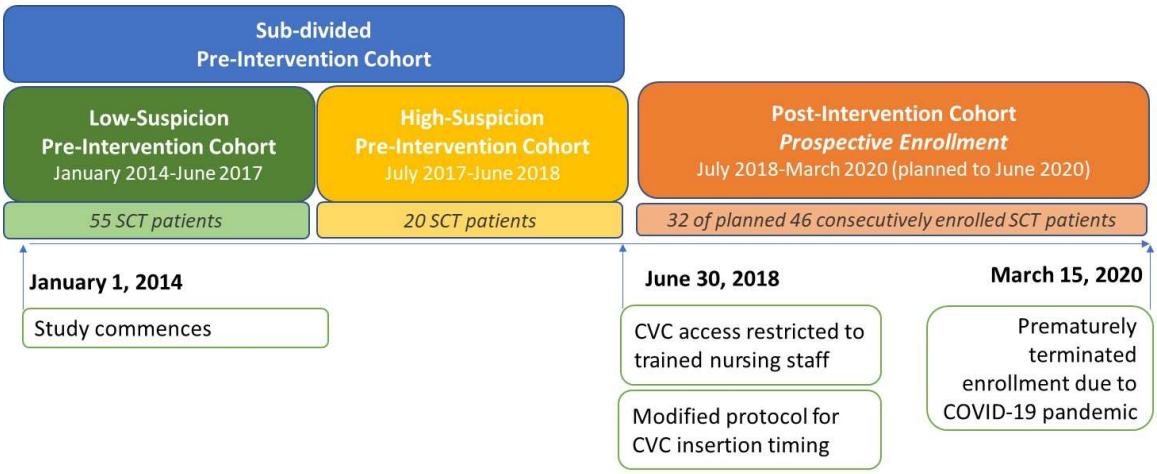

Figure 3.2 Study Timeline with Post-Hoc Analysis

This post-hoc Poisson analysis was conducted for total infectious complications per 1000 catheter-days. The rates were 2.21, 10.84 and 5.50 per 1000 catheter-days respectively. No statistically significant differences were found between the groups (p=0.34), however these differences were highly clinically significant.

An ANOVA (analysis of variance) demonstrated incidence of total infectious complications of 28.3%, 63.4% and 40.6% for these timeframes. The analysis revealed a significant difference in the incidence of the sub-divided pre-intervention group with a mean difference of 35.3% (95% CI 0.06-0.65, p=0.013). The timeframe was explanatory for just 7.6% of the variance between these subgroups. No other statistically significant differences in incidence were found.

4.3 Risk Factors for CR-BSI

4.3.1 Patient Related Risk Factors

Eleven patient-related predictors were included in the univariate analysis, and 1 was statistically significant. Patients undergoing SCT with only a single previous line of chemotherapy had a hazard ratio of 0.114 (p 0.001). Total 90-day prednisone-equivalent corticosteroid dose and use of erythropoietin were not significant. (prednisone p=0.659, erythropoietin p=0.479). Multivariate analysis showed a history of bacteremia as a significant risk factor for CR-BSI with an OR 763.1 (95% CI 1.4-417589.9, p=0.039). Prednisone dose did trend toward significance in multivariate analysis (p=0.11) (Table 4.3).

Table 4.3: Risk Factors for Total CR-BSI

	Univariate Analysis			Multivariate Analysis		
Variable	**HR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* Value**
Gender	1.201	(0.539,2.694)	0.651			
Age (per 10-year increase)	0.838	(0.083,8.103)	0.319	0.519		0.998
Malignancy				2.331		0.802
Multiple Myeloma	1.454	(0.187, 11.280)	0.72			
Mantle Cell Lymphoma	0	(0,0)	0.983			
DLBCL	2.675	(0.328,21.799)	0.358			
Hodgkins Lymphoma	2.449	(0.251,23.881)	0.441			
Follicular Lymphoma	3.846	(0.238,62.233)	0.343			
Transplant Status						
Previous SCT	3.571	(0.810,15.755)	0.093			
History of Bacteremia	1.524	(0.447,5.191)	0.501	763.118	(1.40,417589.90)	0.039
History of Fungemia	20.406	$(0.000,2.13*10^{11})$	0.798			
History of Radiotherapy	1.431	(0.426,4.800)	0.562			
Lines of Chemotherapy				2.137		0.554
1	0.114	(0.021,0.612)	0.011	2.137		0.554
2	0.436	(0.096,1.985)	0.283			
3+	0.179	(0.024,1.324)	0.092			
Total 90-day Prednisone Dose	1	(0.99,1.00)	0.659	0.998	(0.996,1.00)	0.11
Erythropoietin Use	2.068	(0.277,15.442)	0.479			
Days from SCT to PMN > 500	0.849	(0.677,1.064)	0.155			
Type of CVC				0.145		0.986
PermaCath	0.033	(0.004,0.295)	0.002			
Hickmann	0.113	(0.013,1.010)	0.051			
Insertion Site						
Right IJ	0.048	(0.006,0.413)	0.006			
Left IJ	0.081	(0.005,1.395)	0.081			
Mean Days CVC In Situ	0.948	(0.925,0.973)	0	0.94	(0.896,0.986)	0.011
Antibiotic Prophylaxis	1.928	(0.448,8.310)	0.378			
Heparin Impregnated CVC	0.801	(0.353,1.815)	0.595			
Radiologist Level of Training						
Attending	1.359	(0.401,4.607)	0.622			
Exit Site Infection	0.571	(0.212,1.543)	0.27	13.242	(0.766,228.98)	0.076
CR-TLI	0.607	(0.179,2.061)	0.423			
Thrombotic Complication	0.674	(0.200,2.273)	0.525			

DLBCL - Diffuse Large B-Cell Lymphoma, PMN - Polymorphic Nuclear Cells, IJ - Internal Jugular

4.3.2 CVC Related Risk Factors

Eight CVC-related predictive factors were included in univariate analysis, and two were statistically significantly associated with CR-BSI. A significant protective association between Permacath type CVC and CR-BSI (HR 0.03, 95% CI 0.004-0.295, p =0.002) was identified. Likewise, there was a significant protective association between right IJ placement of the CVC and CR-BSI (HR 0.048, 95% CI 0.006-0.413, p=0.006). This is consistent with this location as a clean site predominantly selected as the insertion point in SCT patients as well as ICU and hemodialysis.

Neither antibiotic prophylaxis nor heparin-impregnation of the CVC demonstrated any association with CR-BSI despite their routine use as a prevention mechanism by some interventional radiologists. Additionally, a preceding exit-site infection or tunneled-line infection had no association with the development of CR-BSI.

Multivariate analysis revealed a weak protective association for total days CVC indwelling (OR 0.94, 95% CI 0.896-0.986, p=0.011). Preceding exit site infection did trend towards significance with an OR of 13.24 but with a wide 95% CI (0.77-229.0, p=0.076).

4.4 90-Day Mortality

Throughout the entire study period only a single death occurred in the 90-day follow-up period. The rarity of this event is decidedly below the expected rate and limits the statistical analysis planned. The death observed occurred in the pre-intervention group and thus generates a statistically significant difference in the rate between groups, however this cannot reliably be assessed (Table 8).

Table 4.4: 90-Day Mortality

	Total Population		Infectious Complication		No Infection		P-Value
Total Cases	107		42		65		
Deceased	1	0.93%	1	2.38%	0	0.00%	0.012

4.5 CVC Line Survival Comparison

A Kaplan-Meier survival curve was generated to demonstrate the survival period of CVCs between the pre- and post-intervention cohorts. The resulting curves are below, demonstrating no difference in CVC survival. The pre-intervention cohort has two outliers with extremely prolonged periods with the same CVC remaining indwelling (more than 1400 days in one case) related to either delayed SCT or lines placed primarily for hemodialysis. A sensitivity analysis was performed removing the two longest periods for the pre-intervention group without a change to the outcome (Figure 4.3).

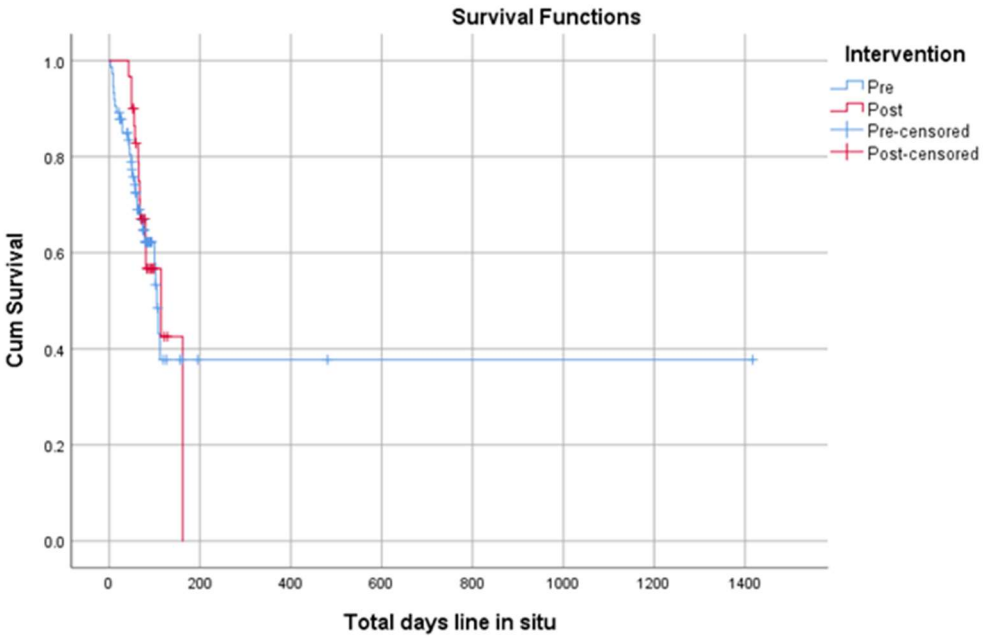

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Figure 4.3: Total CVC Survival Kaplan-Meier Curves for Pre- and Post-Intervention Cohorts

The two curves do separate early suggesting there may be some improvement in CVC survival in the post-intervention group. However, by day 80 the curves overlap. The Mantel-Cox analysis did not show a significant difference between the two curves (p=0.822).

A second Kaplan-Meier analysis was conducted comparing CVC survival in patients with infectious complications against those without. The resulting curves are presented below. As expected, patients without line infections are able to maintain their central venous catheters for significantly longer periods of time (p<0.0001) (Figure 4.4).

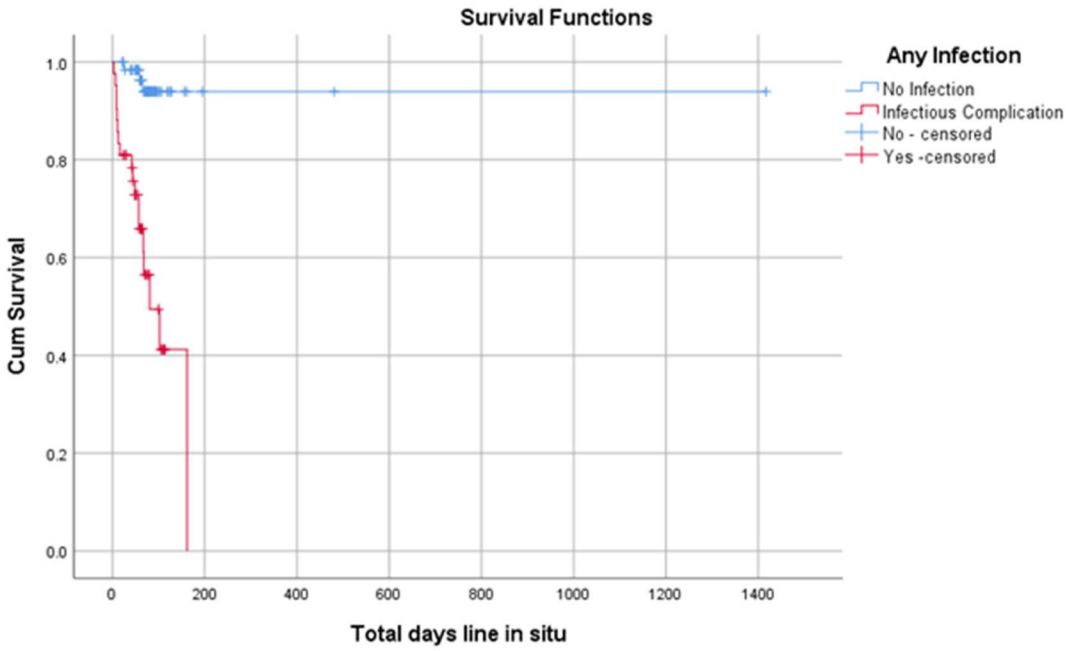

Figure 4.4: Total CVC Survival Kaplan-Meier Curve Comparing No Infection Versus Infectious Complication

4.6 Time from CVC Insertion to CR-BSI

An inverse Kaplan-Meier analysis was conducted to compare the time from CVC insertion to CR-BSI detection. The resulting curves show a significant difference between time to onset of infection (p = 0.003). The curves separate early and remain separate throughout the observation period. The first infectious complication in the post-intervention group occurred 46 days from CVC insertion, meanwhile 14/16 (87.5%) of infectious complications had occurred by that point in the pre-intervention group (Figure 4.5).

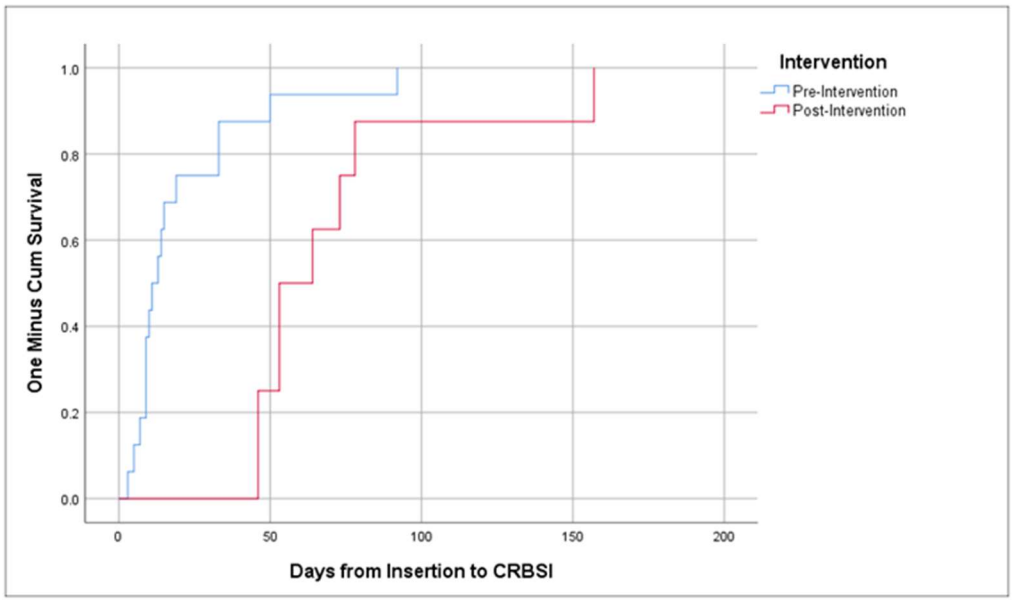

Figure 4.5: Onset of CR-BSI from CVC Insertion Comparing Pre- and Post-Intervention Cohorts

4.7 Time from SCT to CR-BSI

A similar inverse Kaplan-Meier analysis was performed to compare time from SCT to CR-BSI. The analysis excluded two cases where patients experienced an infectious complication in the stem cell collection phase prior to SCT. Both of these events occurred in the pre-intervention period in the period of highest concern for increasing incidence of infectious complications (July 2017-June 2018). These events occurred 39 and 43 days prior to SCT.

The resulting curves are presented below. There was no significant difference between the groups by the Mantel-Cox test ($p = 0.297$) (Figure 4.6).

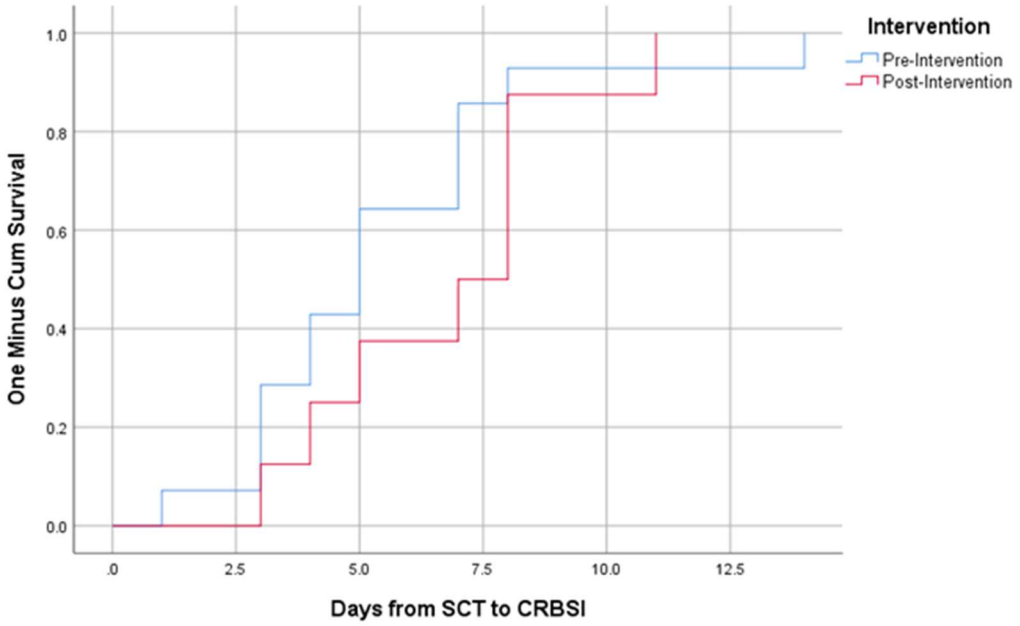

Figure 4.6: Days from SCT to CR-BSI Comparing Pre- and Post-Intervention Cohorts

4.8 Causative Pathogens and Modified CR-BSI

The etiologies of CR-BSI in the total study population are separated in table 9 into two groups of bacteria. There were an equal number of infections caused by these two groups.The first are those typically associated with skin and soft tissue infections that might be considered high risk for causing a CVC-associated infectious complication. The organisms identified in this group are *Staphylococcus aureus* (6), *coagulase negative Staphylococcus* (3), *Rothia* (1), *Staphylococcus lugdunensis* (1) and *Staphylococcus epidermis* (1).

The second group are Gram-negative organisms and those typically found in the oropharyngeal or gastrointestinal tract of humans. It has been proposed that these organisms are more likely to cause a bloodstream infection through an

interruption of the mucosal barrier, as opposed to causing a bloodstream infection by entering the CVC. This is typically considered a complication of graft-versus-host disease, though it can also be caused by chemotherapy, radiation and conditioning agents used in the preparation for SCT.[27] When there is no complaint or examination finding representing gastrointestinal involvement and these organisms are detected, surveillance definitions continue to include them as probable CR-BSI. A previous epidemiological study of CVC infectious complications in SCT patients by Leukenbill *et al.* proposed a modified definition of CR-BSI to exclude these organisms.[21] The organisms in this category encountered in this study population are *Escherichia coli* (6), *Pseudomonas* (2), *Haemophilus influenzae* (1), *Streptococcus salivarius* (1), and *Klebsiella pneumoniae* (2) (Table 4.5).

Table 4.5: Causative Organisms by Blood Culture

Causative Organism	Total Cases	Percentage	Cumulative
Skin Flora	12		
Staphylococcus Aureus	6	25	25
Coagulase Negative Staphylococcus	3	12.5	37.5
Rothia	1	4.2	41.7
Staphylococcus lugdunensis	1	4.2	45.9
Staphylococcus epidermis	1	4.2	50.1
Oropharyngeal & Gastrointestinal Flora	12		
Escherichia coli	6	25	75.1
Pseudomonas	2	8.3	83.4
Haemophilus influenzae	1	4.2	87.6
Streptococcus salivarius	1	4.2	91.8
Klebsiella pneumoniae	2	8.3	100

The study by Leukenbill *et al*. suggested that the reported incidence of CR-BSI could be reduced by 25.8% if the organisms were removed per the modified definition.[21] In our study population the incidence of CR-BSI would be reduced by 50% to 11.2% if organisms were removed per the modified definition (Table 4.6).

Table 4.6: Incidence of Total CR-BSI for the Total Population

	Incident Cases	Incidence
Original Definition of Positive Blood Cultures	24	22.4%
Modified Definition of Positive Blood Cultures	12	11.2%

In cases where culture results represented infections typically associated with skin and soft tissue the mean length of CVC survival was 7.25 days from positive blood culture. In comparison the mean length of CVC survival in patients with organisms excluded under the modified CR-BSI definition was 20.25 days. This mean difference of 13 days approached significance (95% CI -1.16, 27.17, p=0.07).

Chapter 5: Discussion

5.1 Efficacy of Interventions in CVC Infection Prevention

Clinicians suspected an increase in the rate of total infectious complications in SCT patients associated with CVCs in mid-2017 for a period extending to mid-2018. ANOVA analysis of these periods confirms that the rate of incident cases did indeed increase during this period, more than doubling from 28.3% to 63.6%. No clear change was identified to explain this rise in incident cases of infectious complications in this time period. A comparison of the pre-intervention cohort with the post-intervention cohort was unable to demonstrate a reduction in incident cases with the dual intervention of a change in timing of CVC insertion and a restriction in nursing access to CVC devices.

The incidence of CR-BSI infections at this institution were 21.3% and 25.0% in the pre- and post-intervention cohorts. Both groups were similar to the incidence identified in the literature review of 24.7-32%.[20,21,23,24,26]

Analysis of the rate of infectious complications per 1000 catheter days did not demonstrate significant change in the incidence rate with the introduction of the dual interventions. The non-statistically significant improvement in total infectious complications is almost entirely attributable to the improvement in exit site infections. Exit-site infections were not shown to be significant predictors of CR-BSI.

Although a significant difference was not observed in infection rate, the interventions were associated with an increase in the survival time of the CVC. CVC survival time is a surrogate for infection risk, although CVC survival time is also influenced by the clinician's decision to remove the CVC, and this decision may not correlate with infection rate.

The pre-intervention CR-BSI incidence rate in the study was 2.39 per 1000 catheter days while the post-intervention group rose to 3.39. The rate for the entire study population is 2.65 CR-BSI per 1000 catheter days. These incidence rates are much lower than the lowest rates identified in the literature review (5.2-7.5 per 1000 catheter days).[20,21,23,24,26] Other study populations have significantly different baseline characteristics, most notably the studies include allogeneic SCT while this centre only include autologous SCT.

While we observed no difference in the overall length of CVC survival between the pre- and post-intervention cohorts, we were able to detect that line removal was significantly delayed in patients who developed infectious complications. Discussions with clinicians and qualitative review of documentation in patient charts revealed no overt change in clinical practice to delay the removal of CVCs in patients with infectious complications by six weeks or more routinely.

Perhaps then a closer look at the specific interventions might help explain this change in duration of CVC survival from CVC placement. The first intervention that moves forward in time CVC insertion by 4-5 days to a period of relatively less. This period represents 11.1% of the longer CVC survival from CVC placement. It may also be that any transient bacteremia that may occur in the process of CVC insertion is overcome by the immunocompetent patient without overt infection in the post-intervention cohort. Unfortunately, the data such as routine post-CVC placement blood culture were not available in the chart review did not allow further analysis of this hypothesis.

The second intervention restricted nursing access to those nurses with advanced training in how to sterilely access CVCs. In the pre-intervention group any access to a CVC by a nursing professional without advanced training would have been likely to occur in the first days or weeks after line placement while the patient remained in the community prior to admission for SCT. This may explain in part why CR-BSI resulted in earlier CVC termination, however little documentation existed in patient charts regarding any out-of-hospital CVC access preventing analysis to support this hypothesis.

In addition, at the introduction of these policy changes inpatient nurses were made aware of the concern for infectious complications and the changes being made to nursing practice. This knowledge that there was concern and ongoing

monitoring may have enacted the Hawthorne effect contributing to the change in incident rate.

5.2 Risk Factors For CR-BSI

Previous epidemiologic studies of CVC infectious complications in the SCT population have been inconsistent in the risk factors identified. Girard *et al.*, had identified a particular type of CVC, the Groshong catheter, as a risk factor for infection (RR 5.75).[26] This device is not used at our centre. Our study did not identify any particular device as a risk factor but did find that PermaCath devices to have a protective effect (OR 0.03 95% CI 0.004-0.295, p=0.002). PermaCath is the predominant device used at this centre for this indication for CVCs and reduced complications may be a feature of the small population size or radiologist and nurse familiarity with the device rather than device characteristics.

Most CVCs are placed at the right internal jugular vein (IJ). This location is easy to access and clean once the CVC is placed in comparison to other access points such as the inguinal veins. The CVC insertions in this study were completed under controlled conditions. The only cases where alternate sites were used were because of anatomical variations, compromise of the right IJ due to previous CVC placement, or thrombotic complications at that site. The right IJ site was demonstrated to be protective for infectious complications with a hazard ratio of 0.05 (95% CI 0.006-0.413, p=0.006). This supports a previous finding by Dix *et al*. which showed a similar protective effect at this site.[20] No study has

shown a particular insertion site to be associated with increased rates of infectious complication.

A study by Worth *et al* had previously shown a positive association between a history of fungal bloodstream infections and future CVC associated bloodstream infections.[23] In our population previous fungal infections were a rare event with only one identified through the chart review. We therefore found no such association in our study. We did, however, identify a history of bacterial bloodstream infection as a significant risk factor in multivariate analysis with an odds ratio of 763.1, though with an extremely wide 95% confidence interval (1.4-417,589.9, p=0.039). Given that our study is small and underpowered it is difficult to confidently attribute such a strong odds ratio to this risk factor that has not been previously reported. It is, however, a point for future investigation. A more detailed charting process may be able to identify whether particular organisms or sources of bloodstream infections point towards re-infection risk.

Authors of previous studies of risk factors of CR-BSI postulated that degree of steroid exposure may be a predictor of infection. No study had previously examined this risk factor. In our study we choose to examine the total prednisone-equivalent dose received over a 90-day period. This dosing was highly variable as significant steroid doses are included in almost all chemotherapy regimens prior to SCT. Patients who received their final cycles of

chemotherapy close to transplant had high steroid burden. Steroid is part of the conditioning therapy for SCT and often dose reduced in frailer patients, or patients who do not tolerate steroid. As a variable thought to predict immunocompromise with escalating doses, smaller doses may in fact reflect a more physically compromised host. Our study was unable to show an effect of steroid dosing and infectious complication.

Girard *et al*. had also previously identified erythropoietin use as a risk factor for infectious complication.[26] Erythropoietin is a hormone that promotes red blood cell production. The authors postulated that it may be a marker for overall hematopoiesis suppression and patients who may not be able to mount an immune response to infection. Our study was unable to replicate this risk factor, though the confidence interval was again wide and may reflect a study population too small to detect the effect (HR 2.07, 95% CI 0.277-15.44, p=0.479).

Overall the study was able to identify only two modifiable risk factors, both with protective effect - right IJ site for insertion and use of a PermaCath. These are both essentially standard of care at our centre already and do not represent significant opportunities for improvement in practice. The results do encourage more vigilance in looking for signs of infection in patients with a history of bloodstream infection. Further work with larger sample sizes may also help to

demonstrate whether antecedent infections such as exit site and tunneled-line infections are risk factors for CR-BSI.

5.3 Causative Organisms and Modified Definitions for CR-BSI

Like the study by Lukenbill *et al*., our study has identified that a significant number of the infections attributed to the CVC under the current surveillance definitions are not caused by skin flora. It also appears that clinical practice attributes these blood culture results in a similar manner, choosing to preserve CVCs for longer in patients with these culture results (mean difference 13.0 days, p=0.07). It is also important to note that additional positive blood culture results with organisms from the oropharyngeal and gastrointestinal tract were excluded from this study results if sufficient data was documented in the chart to identify a credible source other than the CVC for infection.

5.4 A Note on Notes

In mid-2018 Eastern Health enacted a change from paper nursing and physician notes to electronic. While not part of the original design of the study the principal investigator noted a decline in the fidelity of information, particularly from nursing notes with this transition.

In the paper-based documentation, nursing notes were a rich source of data on the day-to-day integrity of CVCs for admitted SCT patients. Many complications in the study classified as exit site infections were only noted in nursing

documentation, even if treated with topical antibiotics. There was regular documentation of line care performed, the presence of early signs and symptoms of infection and comments on the functionality and performance of CVCs. As charting moved to electronic format the depth of information captured in notes thinned and was more frequently associated with a just a single issue (diet, care, patient-voiced concerns, etc.).

It may be the case that this change resulted in underreporting of exit site infections in the latter phases of data collection.

5.5 Limitations

This study is subject to a number of limitations. With the available sample size, the study was under-powered to answer the primary outcome with statistical significance. The retrospective nature of this chart review limits the data to the quality of the documentation, particularly application of the definitions of exit site and tunneled-line infections and documentation of risk factors. Additionally, there is limited documentation of the occurrences in the interventional radiology suite and almost no documentation of interactions between caregivers and CVCs in the outpatient period between CVC insertion and admission for SCT. These are all sources of information bias within the study.

A second source of limitation within the study is the retrospective design for the pre-intervention group. This makes the control of confounders difficult. It also fails

to allow randomization, making the design unable to identify cause-and-effect relationships.

There are also limitations associated with the study population. First, the overall number of patients treated in Newfoundland and Labrador annually are low in comparison with other hematological oncology centres. This requires a longer time horizon to accumulate a sufficient number of patients to meet sample size to power the study. Over this length of time clinical practice patterns can change, particularly as three physician groups are involved in CVC placement and management (Hematology, Interventional Radiology and Infectious Disease). This is a source of potential bias in the study. Local population factors and clinical practice may limit the generalizability of the data to other centres.

Finally, we need to consider that these populations are not randomly sampled and as such there are many differences in the baseline characteristics of the cohorts that may contribute to the differences observed in outcomes.

5.6 Future Work

This study was small from the outset given the limited patient population at our centre. However, the planned enrollment of this study was truncated by the COVID-19 global pandemic and may have limited the overall utility of the results. The intention is for this study to resume enrollment under a new principal investigator once the pandemic has abated to the point that the SCT program

can safely resume. Hopefully a larger sample size also more robust analysis of risk factors contributing to CR-BSI.

All the epidemiological studies examining the issue of CVC infectious complications in this population are limited to single centre studies. This problem is significant in terms of the incidence of cases in this population and the morbidity and mortality associated with infections. I would suggest that a systematic review and meta-analysis of the existing studies to be a good starting point for establishing more robust and consistent data on the risk factors for these infectious complications. It is important to identify mechanisms to reduce the rate of these infections to protect this population.

Further, in the investigation of the credibility of a modified definition of CR-BSI to eliminate oropharyngeal and gastrointestinal agents I would propose a prospective trial that combined physical examination and imaging findings with culture results to attempt to more definitively identify the source of infections in this population to rule out the CVC as the culprit.

5.7 Conclusions

In summary we have been able to confirm clinical suspicion of a rise in the rate of CVC associated infectious complications in SCT patients at Eastern Health in the period from July 2017 - June 2018. An etiology was not obviously evident for this

increase based on the chart review. In terms of the efficacy of the dual interventions we were not able to demonstrate a statistically significant reduction in infectious complications.

Risk factor analysis identified a novel harmful risk factor for CR-BSI in patients with a history of bacteremia prior to SCT. Previous analysis has failed to identify consistent risk factors in this population; however, this study confirmed a single preceding line of chemotherapy treatment as a protective risk factor.

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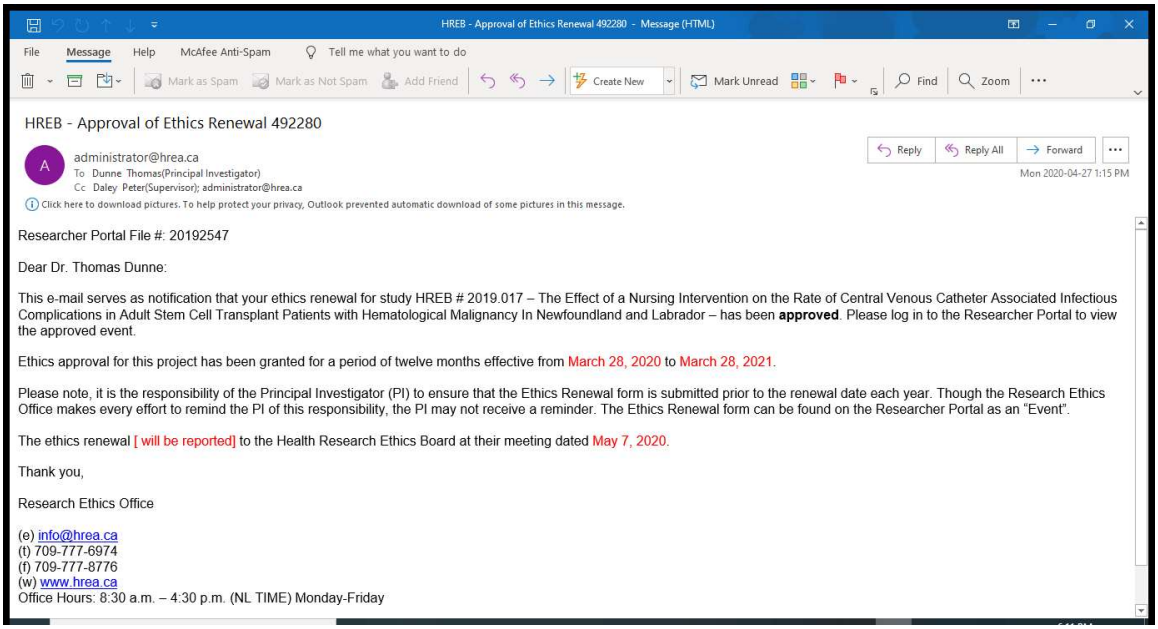
Appendix 1: Ethics Documentation



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HREB - Approval of Ethics Renewal 492280

A administrator@hrea.ca

To Dunne Thomas(Principal Investigator)

Cc Daley Peter(Supervisor); administrator@hrea.ca

Reply Reply All Forward

Mon 2020-04-27 1:15 PM

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Researcher Portal File #: 20192547

Dear Dr. Thomas Dunne:

This e-mail serves as notification that your ethics renewal for study HREB # 2019.017 – The Effect of a Nursing Intervention on the Rate of Central Venous Catheter Associated Infectious Complications in Adult Stem Cell Transplant Patients with Hematological Malignancy In Newfoundland and Labrador – has been **approved**. Please log in to the Researcher Portal to view the approved event.

Ethics approval for this project has been granted for a period of twelve months effective from March 28, 2020 to March 28, 2021.

Please note, it is the responsibility of the Principal Investigator (PI) to ensure that the Ethics Renewal form is submitted prior to the renewal date each year. Though the Research Ethics Office makes every effort to remind the PI of this responsibility, the PI may not receive a reminder. The Ethics Renewal form can be found on the Researcher Portal as an "Event".

The ethics renewal [will be reported] to the Health Research Ethics Board at their meeting dated May 7, 2020.

Thank you,

Research Ethics Office

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May 22, 2019

Dr. Thomas Dunne
88 Gil Eannes Drive
St. John's, NL
A1B 5C4

Dear Dr. Dunne,

Your research proposal *HREB Reference #: 2019.017 "The Effect of a Nursing Intervention on the Rate of Central Venous Catheter Associated Infectious Complications in Adult Stem Cell Transplant Patients with Hematological Malignancy in Newfoundland and Labrador"* was reviewed by the Research Proposals Approval Committee (RPAC) of Eastern Health at a meeting dated May 21, 2019 and we are pleased to inform you that the proposal has been granted full approval.

The approval of this project is subject to the following conditions:

- The project is conducted as outlined in the HREB approved protocol;
- Adequate funding is secured to support the project;
- In the case of Health Records, efforts will be made to accommodate requests based upon available resources. If you require access to records that cannot be accommodated, then additional fees may be levied to cover the cost;
- A progress report being provided upon request.

If you have any questions or comments, please contact Krista Rideout, Manager of the Patient Research Centre at 777-7283 or by email at krista.rideout@easternhealth.ca.

Sincerely,

[redacted]
Farah McCrate
Regional Director, Research and Innovation
Co-Chair, RPAC

FM/rg