Title: Impact of Paired Central and Peripheral Blood Cultures in Children with Cancer

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Abbreviations:

ALL	Acute Lymphoblastic Leukemia
AML	Acute myelogenous leukemia
ANC	Absolute Neutrophil Count
CNS	Central Nervous System tumors
CVL	Central Venous Line
HL	Hodgkin's Lymphoma
ICU	Intensive Care Unit
NHL	Non-Hodgkin's Lymphoma
PICC	Peripherally-Inserted Central Catheter
Port	Port-a-cath

Abstract

Children with cancer require central venous access which carries risk for line-related infections. The necessity of peripheral and central blood cultures is debated for those with fevers. We evaluated and described results for first episode of paired blood cultures from children with cancer who have a central venous line using retrospective database. Blood culture results, laboratory data, and medical outcomes were included. Descriptive analyses of blood culture results and clinical data were performed. There were 190 episodes of paired positive blood cultures with 167 true positive episodes. Of the true positive episodes, 104 (62.3%) were positive in both central and peripheral cultures, 42 (25.1%) were positive in central only cultures, and 21 (12.6%) were positive in peripheral cultures only. Intensive care unit admission within 48 hours after blood cultures (n=33) differed significantly: 28.7% for both central and peripheral, 10% for central only, and 0% for peripheral only (p-value 0.009). Central line removal (n=34) differed by type of positivity but was not significant: 22.1% for both central and peripheral, 23.8% for central only, and 4.8% for peripheral only (p-value=0.15). Peripheral blood cultures provided important medical information yet had differences in short term clinical outcomes. Further evaluation of medical decision-making is warranted.

Introduction

The majority of children with cancer require a central venous line for drawing laboratory studies and administering chemotherapy. However, infectious complications from these devices are common, carrying significant risk for morbidity and mortality due to bacteremia or sepsis.[1-3] When a child with cancer who has a central venous line develops a fever, especially in the setting of neutropenia, a prompt and thorough evaluation, which includes obtaining blood cultures and timely administration of antibiotics, is required.[4-8] The optimal source for obtaining blood cultures, through the central venous line (central) with or without a peripheral venous sample (peripheral), remains controversial, as peripheral cultures in children can be difficult to obtain and painful for the child.[5] Currently, evidence-based recommendations to support obtaining a peripheral blood culture concurrent with a central blood culture in febrile neutropenic children with cancer are lacking.[5,9]

Existing literature suggests there is a wide variation in practice regarding the routine collection of peripheral blood cultures in febrile children with cancer.[5,10,11] Previous studies have found a peripheral blood culture to be the only source of identifying bacteremia in 5.2-17% of patients with paired cultures [12-14] In a single study there were several poor outcomes reported in patients with peripheral only positive blood cultures including 2 intensive care unit (ICU) admissions, 2 deaths, and 1 central line removal.[12]

Given the lack of recommendations, wide practice variation, and paucity of literature there is a critical need to understand the utility of paired cultures in the pediatric oncology population. Therefore, the purpose of this study was to evaluate and compare the identification of

microorganisms by paired peripheral and central blood culture sources. Furthermore, this study described pertinent clinical characteristics and clinical outcomes associated with positive paired cultures in children with cancer. We hypothesized that there would be less incidence of bacteremia identified in peripheral cultures only and there would be less clinical interventions associated with these episodes.

Materials and Methods

Study Design and Setting

We performed a retrospective chart review of children with cancer with at least one positive blood culture, in whom paired blood cultures (at least one peripheral and one central source) were obtained. This study was performed using data from patients treated at Riley Hospital for Children, Indianapolis, Indiana, from July 1, 2013 to June 30, 2017. Riley Hospital for Children is a tertiary care medical center at which 80-90% of all new pediatric cancer diagnoses in Indiana are treated, seeing an average of 200 new cancer patients each year.

Study population/Database development

A database was compiled using the following resources: 1) MedMined Inc. Data Mining Surveillance database, which is a repository of all microbiology laboratory evaluations performed at Riley Hospital for Children, 2) Clinical Research Office (CRO) database of children with cancer at Riley Hospital for Children, and 3) medical chart review.

We obtained all blood culture results from the MedMined database for the study time period including patient name, medical record number, date of culture collection, location collected, source of culture, microbiologic results, and susceptibilities (if applicable). Next, children with cancer were extracted using a clinical patient database maintained by the pediatric oncology

clinical research office. Inclusion criteria for this study required that: the child with cancer had a central venous access line, both a peripheral and a central blood culture were drawn at the same time, and that at least one of the cultures grew a microorganism. It was our clinical practice to obtain cultures from all potential central line lumens and a peripheral culture for all children with cancer who had a fever or signs of clinical sepsis and provide empiric antibiotic coverage at the time of this evaluation. Cultures were excluded if they were not the first positive blood culture for that episode of care or if the patient received antibiotics, other than prophylaxis, within 7 days prior to the blood cultures being drawn.

Definitions

We evaluated the following patient characteristics for each paired culture: age, sex, race/ethnicity, cancer diagnosis, central line type, hospital location where blood cultures were obtained, fever status, and neutropenia status. Age in years was transformed into a categorical variable based on US Census Bureau categories as follows: Ages 0-4, 5-9, 10-14, and 15 and older.[15] Race and ethnicity variables were combined as follows: Non-Hispanic white, Non-Hispanic black, Hispanic, and other. Cancer diagnoses were categorized as: Acute Lymphocytic Leukemia (ALL), Acute Myelogenous Leukemia (AML), solid tumor, central nervous system tumor (CNS), Hodgkin Lymphoma (HL), Non-Hodgkin's Lymphoma (NHL), and other. Central line type included: tunneled central venous catheter (CVL), port-a-cath (port), peripherally-inserted central catheter (PICC) or other (e.g. vascath, pheresis catheter). Patient's location in the hospital was recorded as the unit they were in at the time of obtaining the paired blood cultures (e.g., floor, intensive care unit [ICU]). Patients in the ICU at the time of blood culture were excluded in the analysis of ICU transfers, as their location management would not be affected by

their positive culture. The patient's fever status at the time the paired cultures were obtained was recorded and defined as: a documented temperature of >38°C, a reported fever by patient or caregiver (i.e. no documented fever, but patient/caregiver reported either a objective or subjective fever), or no fever documented. These definitions were based on current clinical practices within the institution at the time of the blood culture samples. The neutropenia status was defined as: if the patient's ANC value was ≥1500/mm^3 they were considered non-neutropenic, mild/moderate (ANC of 501-1499 /mm^3) and severe (≤500 /mm^3).

Blood cultures were categorized based on type of line with positive cultures and presence or lack of contaminants as show in Figure 1. Types of positive paired cultures were classified as: (1) Both central and peripheral if at least one of the microorganism in the episode grew in both the peripheral and central blood cultures (2) Central Only if only the central line culture was positive, or (3) Peripheral Only if only the peripheral blood culture was positive. True positive blood cultures were defined by if either the peripheral or central blood culture grew a microorganism known to be a pathogen causing invasive disease. The definition of a blood culture contaminant was based off the Centers for Disease Control (CDC) and National Healthcare Safety Network definition.[16] Organisms that are commonly considered skin flora (*Corynebacterium* spp, *Bacillus* spp, *Propionibacterium* spp, coagulase negative *Staphylococcus*, *Aerococcus* spp, or *Micrococcus* spp) were considered contaminants and not analyzed with the true positive culture data, unless: (1) the organism was isolated in both culture types (i.e., central and peripheral) at the same blood draw episode or (2) the organism was isolated from the same culture type on separate blood draws (typically within 24 hours).[16] Species of viridans group *Streptococcus* are common skin flora, however, are well known to cause infection in

immunocompromised patients.[17] Viridans group *Streptococcus* species were grouped together and were considered a contaminant only if ≥1 common skin contaminant was found in the same culture (polymicrobial culture), otherwise they were considered a true positive.

Short-term outcomes included transfer to the ICU from either the inpatient floor (within 48 hours of blood cultures being obtained) or directly from the ED (if that was the location of obtaining blood cultures) and if the central line was surgically removed. Both of these outcomes were based on individual or team decision making as we did not have a dedicated clinical practice guideline in place at the time of this evaluation.

Statistical Analysis

Descriptive statistics were used to describe the patient's age, sex, race/ethnicity, cancer diagnosis, central line type, hospital location where blood cultures were obtained, fever status, and neutropenia status. We calculated the proportion of contaminants and true positive blood cultures for the entire cohort, as well as compared them by type of positive paired culture. We described the types and frequency of microorganisms by contaminants and true positive cultures, both overall and by type of positive paired culture. We also evaluated type of true positive paired culture by type of line. We evaluated short-term clinical outcomes including transfer to the ICU and whether the patient had their central line removed, both overall and by type of paired culture. All analyses were performed using SAS 9.4 (Carey, NC) and Microsoft Excel. Comparison of nominal values and p-values were calculated using Fisher's exact test for small sample sizes for ICU transfer, central line removal, and central line type. Chi square was used for overall type of microorganism encounter. All analyses were considered significant at the 0.05 level.

Results

There were a total of 190 paired blood culture episodes with at least one positive culture result from 137 children with cancer. Characteristics of the patient population and paired blood culture episodes are presented in Table 1. The largest age group (in years) was ages 5-9 (29%), followed by ≥15 (28.4%), 0-4 (27.9%), and 10-14 (14.7%). The majority were male (61.6%) and non-Hispanic white (79.5%). The three most common cancer diagnoses were: ALL (33.2%), AML (21.6%), and solid tumor (16.3%). The majority of patients had a central venous catheter (55.3%), followed by a port-a-cath (37.4%), peripherally inserted central catheter (PICC) (6.3%), and other (1.1%). Most cultures were obtained either on the inpatient floor (51.6%) or in the emergency department (30%), while 14.2% were collected in outpatient clinic and 4.2% were in the ICU.

Among the 190 paired blood culture episodes; 104 (54.7%) were positive in both central and peripheral cultures, 58 (30.5%) were positive in central culture only, and 28 (14.7%) were positive in the peripheral culture only. There were 167 paired blood culture episodes determined to be true positives with 104 (62.3%) that were positive in both central and peripheral cultures, 42 (25.1%) that were positive in central only cultures, and 21 (12.6%) that were positive in peripheral cultures only. Notable organisms that grew in peripheral cultures include *Candida albicans*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. There were 42 different types of microorganisms grown in the true positive paired blood culture episodes, presented in Table 2.

There were 33 paired blood culture episodes that grew a microorganism that we considered to be a contaminant. In 10 of these episodes a microorganism considered a true pathogen grew

concurrently with the contaminant. Of the episodes with a contaminant, 6 (18%) were found in a peripheral and central episode, 19 (57.6%) were found in a central episode only, and 8 (24.2%) were found in a peripheral episode only (p=0.01). Among the both central and peripheral episodes, contaminants were found from 5 central cultures and 1 peripheral culture. The types of microorganisms designated as contaminants are listed in Table 3.

True positive paired cultures were compared by line type, as listed in Table 4. Overall, the most positive cultures were from central venous catheters (94/167). Cultures were positive in the peripheral only 13 (61.9%) in children who had ports compared to CVC 7 (33.3%) or PICC lines 1 (4.8%) (p=0.14).

When we investigated the short-term clinical outcomes for patients based on type of true positive paired culture episode, we found differences in both need for transfer to the ICU and line removal (Figure 2). Of the 160 patients that had a paired blood culture taken outside of the ICU, 33 (20.6%) required ICU admission within 48 hours after the blood cultures were obtained. This differed significantly by type of paired culture episode with 29 (28.7%) for both central and peripheral, four (10%) for central only, and 0 for peripheral only (p-value=0.002). The central line was removed in 34 (20.4%) episodes, which also differed by type of positivity but did not meet the level of significance: 23 (22.1%) for both central and peripheral, 10 (23.8%) for central only, and 1 (4.8%) for peripheral only (p-value=0.15).

Discussion

In this retrospective review of children with cancer and central venous access, we found that peripheral blood cultures were the only source to identify the pathogen, including highly virulent organisms (e.g., *S. aureus, C. albicans*), causing true bacteremia in 12.6% of our patient population. Additionally, peripheral blood cultures did not significantly increase the number of contaminants compared to central cultures. These finding add a much needed contemporary cohort to a growing body of literature that highlights the utility of peripheral cultures in the evaluation of children with cancer and fever.[13,14,18,19]

In patients with bloodstream infections, early recognition of sepsis and initiation of targeted antibiotic therapy is critical as mortality increases with each hour of delayed treatment.[20-22] For children with cancer and febrile neutropenia, prompt administration of antibiotics is associated with improved outcomes.[23,24] Though it is common practice to start empiric antibiotics shortly after obtaining blood cultures in these children, the ability to optimize antibiotics based on culture results allows for more targeted, and often superior treatment.[25] With rising rates of antibiotic resistant organisms causing infections and worse outcomes in children with cancer, the ability to select empiric antibiotics with activity against these organisms is increasingly challenging.[26] Additionally, inappropriate use of broad-spectrum antimicrobials not only contributes to patients enduring drug toxicity, increased lengths of stay, and additional costs, but also increases the frequency of antimicrobial-resistant organisms.[20] Thus, by allowing for the early recognition of bloodstream infections and increasing the yield of pathogen identification, as shown in this study, peripheral blood cultures play an important role in the workup of children with cancer and fever.

Though we found that peripheral cultures increase the yield of pathogen identification, the overall impact this has on patient outcomes remains unclear. In our study we found that peripheral only positive cultures did not result in as many additional non-antibiotic related medical interventions as positive central only or positive central and peripheral cultures. This reveals that dedicated prospective evaluation of paired blood cultures in children with cancer is warranted in order to capture and characterize both pertinent clinical features and clinical decision-making. By embarking on a prospective evaluation, all episodes would be able to be captured including outcomes for patients with negative paired cultures. There would also be the opportunity to have further understanding about the clinical reasoning or scenarios in which peripheral cultures are not obtained. Last, more detailed information about those patients with peripheral only positive cultures could be obtained including the proportion which were able to have their antibiotic coverage narrowed and if the duration of therapy was less than if they had received the planned empiric therapy.

It is appreciated that there are several drawbacks to the inclusion of peripheral blood cultures in the evaluation of children with cancer who present with fever or concerns for bacteremia or sepsis that warrant discussion. Children with cancer experience pain during their disease treatment including from venipuncture for peripheral cultures.[27] Additionally, the potential for identifying a contaminant in peripheral blood cultures may add additional hospital visits or inpatient length of stay, increasing the burden to the patient and caregiver. Importantly, in this study we found that the proportion of contaminants from peripheral blood cultures was not higher compared to central cultures.

Taken all together, clinicians must weigh both the positive and negative consequences of obtaining peripheral blood cultures when caring for children with cancer with fever. Given these challenges, pediatric oncology providers remain divided regarding the inclusion of peripheral blood cultures as a part of fever work-up, which has led to practice variation. Centers who omit peripheral cultures argue that there have not been negative effects of doing so, however without a study dedicated to this it would be difficult to be certain that no adverse events had occurred secondary to missed bloodstream infections.[12] A survey of providers at the Hospital for Sick Children in Toronto, Canada revealed that an overwhelming majority (97%) of providers would opt to include a peripheral blood culture if omitting one would constitute a risk of >10% chance of missing a true blood stream infection.[12] If ultimate management of the clinical course would not change, providers opinion regarding the inclusion of a peripheral blood culture may be altered. Therefore, the impact of positive peripheral only cultures on final medical decision making needs to be further studied.

Our study does have limitations. First, this is a single institution retrospective study. Though we evaluated a relatively large cohort of children over several years, generalizability to other centers may be limited. Second, episodes of bacteremia that occurred, but did not include a peripheral culture in the evaluation were not included in this study, therefore the prevalence of bacteremia could not be determined in this population. We were also not able to discern the clinical reasoning for not obtaining peripheral cultures as could be done in a prospective study. Specifically, there is a possibility that non-paired culture episodes involved children who were considered lower risk and therefore providers opted to omit a peripheral blood culture for that reason. If this were the case, it is possible our study selected for children at higher risk of blood stream infections. The short-term outcomes we chose to investigate may have some variation

between providers, but we felt our hospital system practiced in a similar function throughout the study period so were comfortable with the potential for small variability. We did not address mortality in this study due to the complexity of conditions among these patients and inability to fully characterize their concurrent comordities due to the retrospective nature of this study. Additionally, variation in diagnostic microbiology technology and techniques among different centers may affect the ability to identify pathogens and this must accounted for when comparing culture types.[28]

In conclusion, the decision whether to obtain a peripheral blood culture in children with cancer who have a central line is challenging. While there are some potential drawbacks to peripheral blood cultures, we have shown that peripheral cultures significantly increase the yield of pathogen identification without a large number of contaminants compared to central blood cultures. This has potentially important implications regarding ability to accurately identify all episodes of bacteremia and improve antibiotic stewardship among these patients. Further retrospective investigations focusing on the impact of peripheral blood cultures on long-term antibiotic management and medical decision-making are warranted. Prospective studies can utilize the results of this study to identify important elements for collection such as clinically reasoning of not obtaining a peripheral culture, information regarding outcomes for those with negative cultures, and comparisons by type of microorganism.

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Figure Legend:

Figure 1. Diagram of inclusion and exclusion of blood cultures to create database of paired blood cultures with at least 1 positive culture

Figure 2. Short-term clinical outcomes based on type of positive paired blood culture episode

Table 1. Characteristics of patient population and paired blood culture episodes

Characteristics	N	%
Age at time of paired culture		
0-4 years	53	27.9
5-9 years	55	29.0
10-14 years	28	14.7
≥15 years	54	28.4
Sex		
Male	117	61.6
Female	73	38.4
Race/Ethnicity		
Non-Hispanic White	151	79.5
Non-Hispanic Black	20	10.5
Hispanic	16	8.4
Other	3	1.6
Cancer Diagnosis		
Acute Lymphoblastic Leukemia	63	33.2
Acute Myelogenous Leukemia	41	21.6
Solid Tumor	31	16.3
Central Nervous System Tumor	21	11.1
Hodgkin Lymphoma	4	2.1
Non-Hodgkin Lymphoma	13	6.8
Other	17	8.9
Central line type		
Port	71	37.4
Central Venous Catheter	105	55.3
PICC	12	6.3
Other	2	1.1
Location blood culture obtained		
Emergency Department	57	30.0
Inpatient floor	98	51.6
PICU	8	4.2
Clinic	27	14.2
Fever Status		
Documented	170	89.5
Reported	16	8.4
None	4	2.1
Neutropenia Status		
Non-Neutropenic ≥1500/mm^3	47	24.7
Mild/Moderate 501-1499/mm^3	10	5.3
Severe ≤500/mm^3	133	70.0

Table 2. Types of true microorganisms by type of positive paired culture

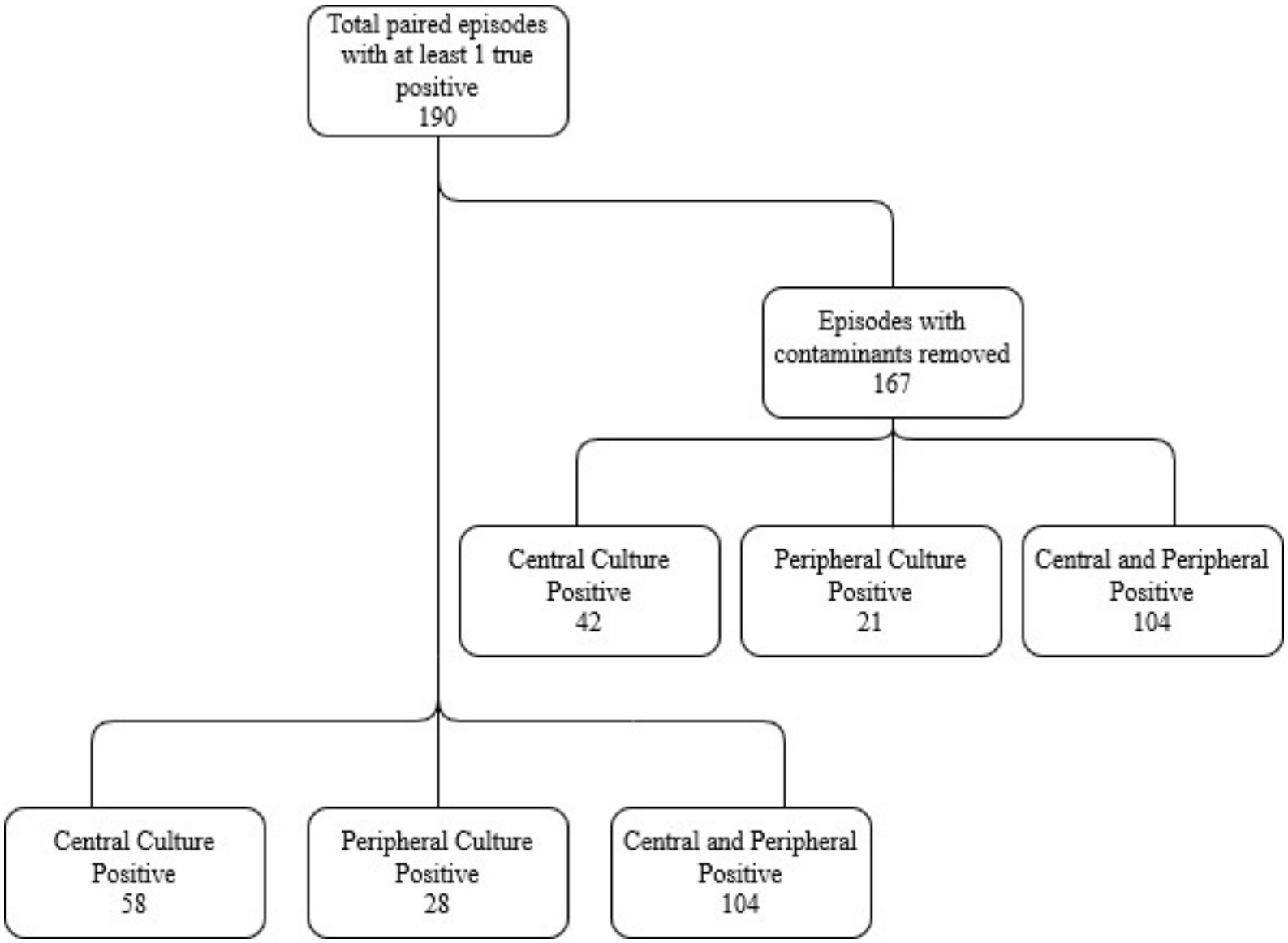
Microorganism (by genus) Total N of microorganisms=195 (42 types)	**Both central and peripheral** N of microorganisms=115 (26 types)	**Central only** N of microorganisms=52 (20 types)	**Peripheral only** N of microorganisms=28 (16 types)
Gram Positive	68(59.13)	23(44.23)	17(60.71)
Bacillus	4(3.48)	1(1.92)	0
Capnocytophaga	0	0	3(10.71)
Clostridium	1(0.87)	1(1.92)	0
Corynebacterium	0	1(1.92)	1(3.57)
Enterococcus	3(2.61)	0	0
Gemella	0	0	1(3.57)
Listeria	1(0.87)	0	0
Rothia	2(1.74)	2(3.85)	1(3.57)
Staphylococcus	22(19.13)	8(15.38)	2(7.14)
S. aureus	8(6.96)	1(1.92)	2(7.14)
Coagulase negative *Staphylococcus*	14(12.17)	7(13.46)	0
Streptococcus	34(29.57)	10(19.23)	7(25)
Viridans group *Streptococcus*	24(20.87)	10(19.23)	5(17.86)
Nutritionally variant S*treptococcus (Granulicatella, Abiotrophia*)	1(0.87)	0	2(7.14)
Gram Negative	44(38.26)	28(53.85)	10(35.71)
Acinetobacter	1(0.87)	0	0
Aeromonas	0	1(1.92)	0
Buttiauxella	0	1(1.92)	0
Campylobacter	1(0.87)	0	0
Citrobacter	0	1(1.92)	1(3.57)
Enterobacter	12(10.43)	3(5.77)	2(7.14)
Escherichia	5(4.35)	6(11.54)	3(10.71)
Fusobacterium	0	2(3.85)	0
Haemophilus	1(0.87)	0	0
Klebsiella	14(12.17)	6(11.54)	0
Leptotrichia	0	0	1(3.57)
Neisseria	1(0.87)	2(3.85)	0
Pantoea	0	1(1.92)	0
Pseudomonas	7(6.09)	4(7.69)	2(7.14)
Rhizobium	0	1(1.92)	1(3.57)
Serratia	1(0.87)	0	0
Stenotrophomonas	1(0.87)	0	0
Fungi	3(2.61)	1(1.39)	1(3.57)
Candida	3(2.61)	1(1.39)	1(3.57)

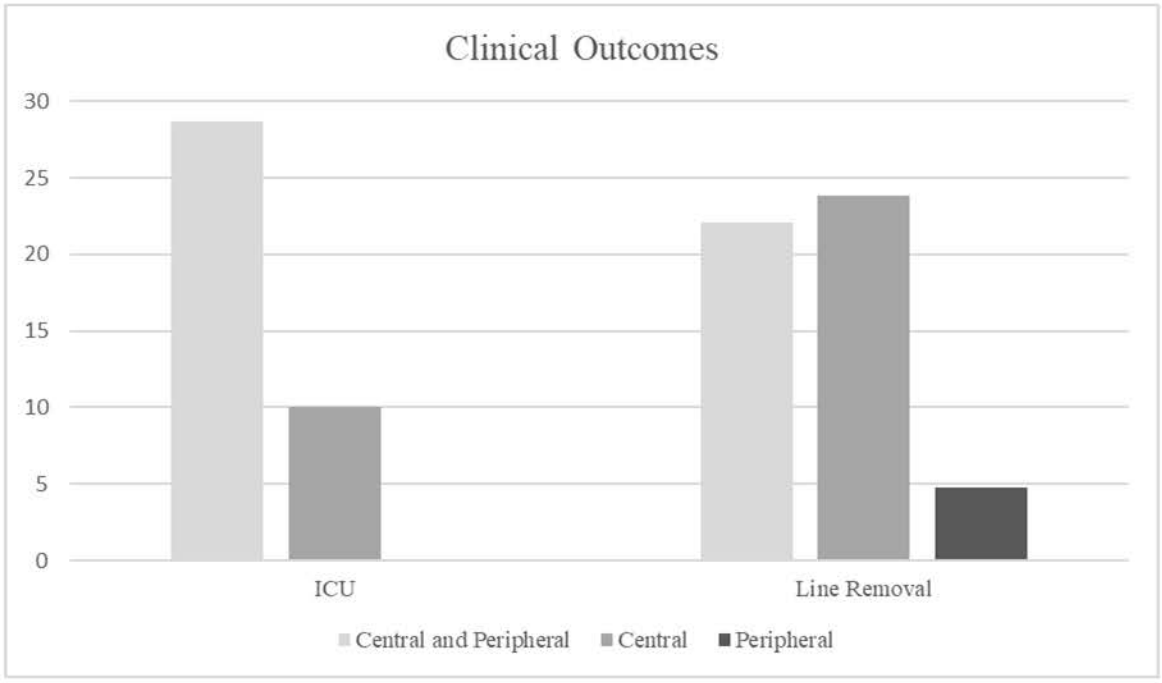
Table 3. Types of contaminant microorganisms by type of positive paired culture

Microorganism Total N of microorganisms=33 (4 types)	**Central only** N of microorganisms=24 (4 types)	**Peripheral only** N of microorganisms=9 (4 types)
Bacillus species	2(8.33)	1(11.11)
Micrococcus species	3(12.50)	1(11.11)
Staphylococcus species (coagulase negative)	15(62.50)	6(66.67)
Streptococcus Viridans Group	4(16.67)	1(11.11)

Table 4. Overview of true positive blood culture by line type

Line Type N=167	**Central only** N=42	**Peripheral only** N=21	**Central and Peripheral** N=104
Port	11 (26.2)	13 (61.9)	36 (34.6)
Central Venous Catheter	27 (64.3)	7 (33.3)	60 (57.7)
PICC	4 (9.5)	1 (4.8)	7 (6.7)
Other	0 (0)	0 (0)	1 (1.0)


Total paired episodes with at least 1 true positive
190
Episodes with contaminants removed
167
Central Culture Positive
42
Peripheral Culture Positive
21
Central and Peripheral Positive
104
Central Culture Positive
58
Peripheral Culture Positive
28
Central and Peripheral Positive
104


Clinical Outcomes
30
25
20
15
10
5
0
ICU
Line Removal
Central and Peripheral
Central
Peripheral