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Incidence and Risk Factors of Bacterial and Fungal Infection During Induction Chemotherapy for High-Risk Neuroblastoma

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Abstract

High-risk neuroblastoma is an aggressive childhood cancer with poor outcomes. Treatment begins with an induction phase comprised of intense multi-agent chemotherapy with the goal of maximally reducing tumor bulk. Given the high intensity of induction chemotherapy, neutropenic fever and infectious complications are common, however the actual incidence is difficult to determine from clinical trial reports.

We performed a retrospective review of infection related complications in 76 children treated for high-risk neuroblastoma at Texas Children's Hospital. Medical records were reviewed for demographics, febrile neutropenia (FN) episodes, presence and type of bacterial and fungal infections, and potential risk factors for infection.

Fifty-seven percent of patients developed one or more serious bacterial or fungal infections during induction chemotherapy. Additionally, over 75% of patients had at least one admission for FN. Risk factors for developing any infection included female sex, *MYCN* amplification, and having Medicaid. Patients with external central venous catheters and those requiring parenteral nutrition had higher rates of bacteremia or fungemia. Each cycle, 50% were readmitted for either FN or infection. The overall burden of infectious complications was high, with 70% having two or more unplanned admissions for infection or FN.

The incidence of febrile neutropenia and serious bacterial and fungal infections during induction chemotherapy for high-risk neuroblastoma is high. Most patients had at least 2 additional hospitalizations for infectious complications. Risk factors including female sex, *MYCN* amplification, payer status, and type of central access were associated with higher rates of infection in this cohort.

Keywords

neuroblastoma; infection; chemotherapy; bacterial; fungal; febrile neutropenia

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Introduction:

Neuroblastoma is the most common solid tumor in children, affecting nearly 700 children per year in the United States [1]. Approximately 50% of patients are considered high-risk because of advanced disease or adverse biologic features of their tumor. According to the international neuroblastoma risk group (INRG) classification, high-risk neuroblastoma includes tumors with *MYCN* amplification, metastatic tumors in children over 18 months of age, and metastatic tumors in children less than 18 months with 11q aberrations [2]. Over the last decades, survival has improved for these patients as a result of increases in intensity of therapy, using a multimodal approach with chemotherapy, surgery, radiation therapy, autologous stem cell transplant, immunotherapy and differentiating agents.

Infections are well known to cause significant morbidity and mortality in immunocompromised pediatric oncology patients; particularly central line associated blood stream infections (CLABSIs). The impact of CLABSI and other serious infectious complications have been well documented in pediatric leukemia [3–6], but similar studies specific to neuroblastoma have not been reported. The majority of published information on infectious complications of neuroblastoma treatment comes from the clinical trial literature. Recent large cooperative group clinical trials report infections rates of 17% to over 30% for various high-risk induction chemotherapy regimens [7–10]. However, clinical trial reporting may underestimate the true incidence of infectious complications [11] and lacks detailed information related to the numbers and types of infections encountered. Clinical trials often utilize the “worst grade/severity” approach reporting only the most severe common terminology for adverse events (CTCAE) grade of toxicity [12] per patient per type of toxicity within the given time period. For example, a patient may have had several grade 3 or 4 infections during a given reporting period, but only the most severe grade 4 infection is reported for that time period. This approach does not reflect multiple or sequential events, thus under-representing the true toxicity of a given regimen [13]. Furthermore, comparing infectious complications between studies is challenging because reporting periods vary.

No study has described the burden of infections and febrile neutropenia at the patient level across the entirety of an induction chemotherapy regimen. We therefore examined the spectrum of febrile neutropenia and bacterial and fungal infections as well as potential risk factors throughout the induction phase of chemotherapy in high-risk neuroblastoma patients at our center. Our primary objective was to describe the rates and etiologies of infections requiring hospitalization in patients with high-risk neuroblastoma undergoing induction chemotherapy. Our secondary objectives were to determine the rate of hospitalization for febrile neutropenia and to identify the associated risk factors for infection and febrile neutropenia in this population.

Methods and Patients:

This study was approved by the Baylor College of Medicine institutional review board. We performed a retrospective chart review of all patients who were diagnosed with high-risk neuroblastoma and underwent induction chemotherapy at Texas Children’s Cancer Center between January 1, 2002 and January 1, 2015. Subjects were identified by querying clinical

databases at Texas Children's Hospital for pathologic diagnosis of neuroblastoma or ganglioneuroblastoma from biopsy and resection specimens. The electronic medical record was reviewed to determine date of diagnosis and risk group, and those diagnosed after January 1, 2002 and identified as high-risk by their treating oncologist were included. Only patients who were treated entirely at Texas Children's Hospital on a 5-cycle induction chemotherapy with each cycle followed by prophylactic myeloid growth factor were included.

The medical record for each subject was reviewed for demographic information (sex, race/ethnicity, age at diagnosis, and insurance payer), whether the patient had an external central venous access device at any point during induction (excluding pheresis catheter for stem cell collection only), and whether parenteral nutrition was given during induction. Each bacterial or fungal infection requiring a hospitalization or prolonging a hospitalization was captured including organism and site. Finally, febrile episodes without positive organism identifications were also identified.

Definitions:

The definition of infection included any documented bacterial or fungal infection for which the patient required intravenous antibiotics or antifungals. Viral infections were not included in this study. Additionally, culture negative sepsis events, i.e. fever with hemodynamic instability resulting in admission to the ICU but without an organism identified, were considered infections. Febrile neutropenia (FN) episodes included febrile events with absolute neutrophil count (ANC) $<1000/\mu\text{L}$, either resulting in an admission or occurring in patients already hospitalized for other reasons, in which no source of infection was identified. Fever during administration of a blood product that did not persist were excluded as were admissions for fever with no source identified and $\text{ANC} > 1000/\mu\text{L}$.

Statistical analysis:

Demographics and clinical factors including age, sex, race, ethnicity, *MYCN* amplification, year of diagnosis, venous access type, and use of parenteral nutrition were tabulated using descriptive statistics. Logistic regression was used to identify associations between these variables and infectious complications including bacterial and fungal infections and FN. All analyses were performed using STATA software version 12.0. Analyses were performed using two-tailed comparisons when possible and were considered statistically significant if $p < 0.05$.

Results:

Patient Inclusion and Characteristics

Ninety-eight patients were identified as having high-risk neuroblastoma in the indicated time period. Thirteen patients were excluded due to treatment on an institutional clinical trial that did not include prophylactic myeloid growth factor for the first two cycles. One patient was excluded due to reduced intensity of chemotherapy due to pre-existing cardiomyopathy, and one patient died prior to initiation of chemotherapy. Seven patients were excluded for receiving a portion of induction chemotherapy at an outside hospital. Seventy-six subjects

were included in the final analysis. Table 1 shows patient demographics and clinical characteristics. Subjects were initiated on five cycle induction chemotherapy regimens. The order of chemotherapy combinations administered differed, but the regimens were similar in intensity. (Table 2) Seventy subjects completed all five cycles and six were stopped early either due to unacceptable toxicity, death, or progressive disease.

Bacterial and Fungal Infections

Fifty-seven percent of patients developed one or more serious bacterial or fungal infection during their entire course of induction chemotherapy, and 21% had two or more infections (Figure 1). During any individual cycle of chemotherapy, an average of 19% (range 16–24%) of patients had a bacterial or fungal infection (Figure 2). The highest rate of infections occurred after cycle 4 (24%), when most patients at our center had surgical resection of their remaining tumor. Blood stream infections were the most common type of infection, with gram-positive organisms predominating (Figure 3). Fungemia was the least common type of blood stream infection, and there were no episodes of invasive fungal disease of the skin and subcutaneous tissues, sinopulmonary tract, central nervous system or other solid organs. Only two patients (2.6%) died due to infection during induction chemotherapy. The first death occurred in an 11-month-old who developed peritonitis due to a small bowel perforation after cycle 1 and had a concomitant central line infection with *Staphylococcus aureus*. The second patient was a 23-month-old who developed typhlitis, bowel necrosis and *Clostridium perfringens* sepsis following cycle 5 of induction chemotherapy.

The rate of hospitalization for febrile neutropenia (FN) was high in this cohort, with 78% of patients requiring at least one hospitalization for FN. Forty-four percent of patients had two or more hospitalizations for FN (Figure 1). When analyzed per cycle, an average of 30% (range 11-39%) of patients in each cycle were hospitalized for FN (Figure 2).

Risk factors for bacterial and fungal infection

In univariate analysis, children under age 3 years at diagnosis, females, and those with *MYCN* amplified tumors were more likely to have bacterial and fungal infections (Table 3). Patients with private insurance were less likely to have an infection compared to those with Medicaid ($p=0.01$). Females were significantly more likely to have a urinary tract infection compared to males. Females were also 1.8 times more likely to have two or more infections compared to males, ($p=0.006$, 95% CI 0.51, 3.13). *MYCN* amplification was associated with an increased risk of infection. However, when broken down per cycle, this overall increased risk was due to an increased risk of infection for *MYCN* amplified patients after cycle 1 of chemotherapy (RR 1.45, $p=0.04$, 95% CI 0.6, 2.8). In other cycles, the risk of infection for *MYCN* amplified patients was not increased. Other demographic factors including race, ethnicity, and year of diagnosis were not found to be significant risk factors for bacterial and fungal infections.

In multiple logistic regression analysis, female sex and payer remained significant. For the purposes of multiple logistic regression analysis, use of parenteral nutrition was excluded due to a collinearity between payer status and *MYCN* status which could not be rectified. Females were 1.7 times more likely to have an infection compared to males, and those with

private health insurance were less likely to have infections compared with Medicaid. (Table 4)

When the analysis was limited to blood stream infections only, patients with an external central venous catheter were 2.13 times more likely to develop infection compared to those with a totally implantable venous access device ($p=0.007$) (Table 3). Additionally, patients who were diagnosed between 2009–2015 were less likely to have a blood stream infection than those diagnosed from 2002–2008 ($p=0.027$). However, this different risk by treatment era can be explained by the clinical use of fewer fully implantable venous access devices being placed in the earlier time frame. In the 2002–2008 era, 100% of patients had an external line at some point during induction, while from 2009–2015, only 44% ever had an external line. The need for total parenteral nutrition was associated with a higher risk of blood stream infection ($p=0.045$). Those with *MYCN* amplified tumors were again more likely to have blood stream infection than those with non-amplified tumors ($p=0.008$). In multiple logistic regression analysis, *MYCN* amplification remained significant with a relative risk of 1.3. (Table 4)

Risk Factors for Febrile Neutropenia

Univariate analysis demonstrated that patients with private insurance were more likely to be hospitalized for FN than those with Medicaid (Table 3), however, this was not significant in multiple logistic regression analysis and may be due to more patients with Medicaid having increased likelihood of hospitalization for infections, and therefore fewer hospitalizations for FN. No other variables were significantly associated with risk of FN.

Burden of Infection or Febrile Neutropenia

The combined rate of hospitalizations for infectious complications including FN or infection was high. On average, each patient in our cohort incurred 2.3 additional hospitalizations or prolonged hospitalizations for FN or bacterial or fungal infection during induction. For those who completed all 5 cycles of chemotherapy, 96% had at least one additional hospitalization or prolongation of prior hospitalization for either FN or bacterial or fungal infection. Seventy percent had 2 or more episodes of infectious complications.

Discussion

Infectious complications are common during all intensive chemotherapy regimens, including high-risk neuroblastoma induction chemotherapy. In this single-institution, 13-year retrospective review, we demonstrate that over half of patients developed at least one serious infection during this phase of therapy, and nearly 40% had at least one blood stream infection. Furthermore, nearly 80% had at least one episode of febrile neutropenia for which they were hospitalized. Overall this review suggests the burden of infectious complications associated with high-risk neuroblastoma chemotherapy may be greater than indicated on clinical trial reports.

Several factors were found to influence the risk of having a serious bacterial or fungal infection, blood stream infection, and FN in our population and are worthy of further study. Female sex was associated with higher rates of infection overall, due to the increased risk of

urinary tract infections, known to be more common in girls in the general pediatric population [14, 15]. Interestingly, having private insurance was found to be protective for infections overall, but not protective for blood stream infections. Reasons for this affect are not immediately obvious from our data, however two theories arise that may be worthy of further investigation. First, supportive services such as home health care could differ between our Medicaid and private payer populations resulting in different infection outcomes. Second, and more likely, is that insurance status is a proxy for socio-economic status and other social determinants of health that are difficult to assess retrospectively. Such factors as crowded housing or differential medical health literacy, may contribute to an increased risk of infection. Parenteral nutrition and insurance status demonstrated multicollinearity in our model. Parenteral nutrition is a known factor associated with increased central line infections in other oncologic studies [16], but its effect was increased when controlled for payer. It is possible that knowledge of the payer status led to differential decision-making by the provider, or was related to a bias about social needs. This affect may be worth future investigation. Additionally, *MYCN* amplification was associated early in induction with a higher rate of both infection overall and blood stream, perhaps suggesting a difference in clinical presentation or immune-competence of these patients.

Infectious complications including FN and bacterial and fungal infections represent a large burden to patients and families as well as the healthcare system in the form of additional or prolonged hospitalizations, each with exposure to broad spectrum antibiotics [17]. In our cohort, after each cycle of chemotherapy, 50% of patients were readmitted for either FN or bacterial or fungal infection. By the end of 5 cycles, most patients had 2 or more and 40% had 3 or more additional admissions for one of these complications. Our data may help providers set expectations of treatment complications, helping families cope with treatment [18, 19]. When presenting a treatment plan to patients and families, providers can prepare them for the likelihood of having at least 2 additional hospitalizations due to infectious complications during the induction period.

The number of intravenous (IV) antibiotic exposures in these patients was higher than we anticipated. Emergency department, clinic and home antibiotic exposures were not evaluated in this study, suggesting the concentration of antibiotic exposure is even higher. In an era of increasing antibiotic resistance and antimicrobial stewardship being used as a direct measurement of quality, this finding represents an area of potential further investigation and improvement. It should be noted that most of these infections do not fit the formal quality definitions of nosocomial CLABSI and are unlikely to be preventable by current inpatient-focused process improvement efforts. Efforts to define a low risk febrile neutropenia categorization have resulted in FN treatment guidelines allowing for outpatient treatment of FN, reducing the burden of admission on hospitals and providers as well as families, and potentially reducing the risk of nosocomial infection leading to a prolonged stay or readmission [20]. Furthermore, standardizing practice regarding appropriate narrowing and duration of antibiotic coverage should continue to be a focus of pediatric hematology/oncology training and continuing education. Over the past decade, however, intensity and duration of neuroblastoma therapy has increased with additional cycles of chemotherapy added to induction regimens as well as additional consolidation and maintenance phases requiring prolonged need for central venous catheters possibly increasing exposures to

antibiotics, altering the individual microbiome, and leading to increased complications such as fungal infections and *C. difficile* colitis.

The rates of bacterial and fungal infection and FN requiring intravenous antimicrobials in this cohort are higher than those reported in the clinical trial literature for modern induction therapy regimens. However, it is difficult to compare our data to that of the clinical trial literature as all bacterial and fungal infections requiring intravenous antimicrobials were accounted for in this study, compared with variable reporting in the clinical trial literature, which may include only the most severe of infectious complications during the reporting period, or only the rates per reporting period rather than on a per patient level for the entire induction regimen.

Data were collected retrospectively for this study, subjecting it to the usual limitations of retrospective review. Additionally, while all patients were treated on a similarly intense 5 cycle induction regimen, patients were not treated uniformly. We were therefore unable to attribute rates of infection and FN to specific chemotherapeutic agents. Most of these patients were not enrolled in cooperative group clinical trials, therefore, we are unable to compare adverse event reporting with this chart abstraction. Since our aim was to determine the burden of infectious complications in induction, we wanted to include all admissions for a diagnosis of febrile neutropenia, regardless of the specific cutoff of absolute neutrophil count. We included all admissions for fever with ANC<1000/ μ L, although we realize that many patients fitting this definition were not admitted to the hospital. A practice guideline to recognize and intervene in potential septic shock was implemented in our institution's emergency center during the time frame of this study [21], and may have increased the number of patients admitted for FN, particularly those with ANC between 500–1000/ μ L. Viral infections were not included in this study. It is probable that many patients admitted for FN had viral infections, particularly viral upper respiratory infections. Viral testing is inconsistent amongst providers and seasons. In winter months, many patients are tested for influenza and respiratory syncytial virus, however, patients with similar symptoms in summer months are often not tested. These inconsistencies made viral infection analysis unreliable. Finally, our study examined the risk factors for infectious complications in high-risk neuroblastoma patients receiving induction chemotherapy and may not be generalizable to the remainder of therapy or to other pediatric oncology patients.

Bacterial and fungal infections as well as febrile neutropenia are common complications encountered in patients undergoing induction chemotherapy for high-risk neuroblastoma, however, mortality from these complications is low. Females, those with *MYCN* amplified tumors, and those with Medicaid may be at particular risk, however, all families should be prepared for the likelihood of at least two additional hospitalizations for these complications. As neuroblastoma therapy becomes longer and more intensive, the burden of additional and prolonged hospitalizations as well as increased antibiotic exposures should be considered.

Abbreviations

CLABSI	Central line associated blood stream infection
CTCAE	Common Terminology Criteria for Adverse Events

FN	Febrile neutropenia
ANC	Absolute neutrophil count
TPN	Total parenteral nutrition

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Figure 1. Percent of subjects with 0, 1, 2 or greater than or equal to 3 bacterial/fungal infections or febrile neutropenia episodes over 5 cycles of induction chemotherapy

Figure 2.
Rate of infections or febrile neutropenia following each cycle

Distribution of Infections

Figure 3.

A) Distribution of infection types B) Distribution of organisms causing blood stream infections

TABLE 1

Patient and Treatment Characteristics

Category	N	%
Sex		
Male	47	61.8
Female	29	38.2
Race/Ethnicity		
NHW	40	53
HW	18	24
NHB	10	13
NH-other	5	7
Unknown	3	4
Age at diagnosis (months)		
<18 m	12	15.8
18–36m	20	26.3
36m–60m	25	32.9
60–120m	14	18.4
120+ m	5	6.6
MYCN status		
Non-amplified	35	46.1
Amplified	35	46.1
Unknown	6	7.9
Year of diagnosis		
2002–2008	40	52.6
2009–2015	36	57.4
Payer		
Medicaid	28	36.8
Private	40	52.6
Other	8	10.6
Type of central line		
Totally implantable	26	34.2
External line (PICC, DL tunneled or phoresis) *	50	65.8
Received TPN		
No	50	65.8
Yes	26	34.2

* refers to patient having external line at any point in induction therapy

refers to patient having external line at any point in induction therapy

Abbreviations: DL: double lumen; HW: Hispanic White; NHB: Non-Hispanic Black; NH-other : Non-Hispanic Other; NHW: Non-Hispanic White; PICC: Peripherally-inserted central catheter; TPN: total parenteral nutrition

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TABLE 2

Chemotherapy Combinations and Incidence of Infection and Febrile Neutropenia following that combination

Chemotherapy Combination	Number of Cycles Administered	Incidence of Infection	Incidence of FN
Vincristine/Doxorubicin/Cyclophosphamide	147	25.9%	42.2%
Cisplatin/Etoposide	87	20.7%	33.3%
Ifosfamide/Etoposide	66	15.2%	9.1%
Carboplatin/Etoposide	62	12.9%	9.7%
Other	4	25%	25%

Cisplatin/Etoposide: Cisplatin 40 mg/m²/day x 5 days, Etoposide 200 mg/m² x 3 daysVincristine/Doxorubicin/Cyclophosphamide: Vincristine 1.5 mg/m² x 1 day, Doxorubicin 60 mg/m² x 1 day, Cyclophosphamide 2000 mg/m² x 2 daysIfosfamide/Etoposide: Ifosfamide 1800 mg/m² x 5 days, Etoposide 100 mg/m² x 5 daysCarboplatin/Etoposide: Carboplatin 500 mg/m² x 2 days, Etoposide 150 mg/m² x 3 days

TABLE 3

Univariate analyses for all infections, blood stream infections only, and febrile neutropenia

		All infections			Blood Stream Infection			Febrile Neutropenia		
		RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
Sex	Male									
	Female	1.4	0.33-2.39	0.009	0.45	-0.59-1.4	0.35	-1.1	-0.01-2.21	0.052
	NHW									
Race/Ethnicity	HW	1.15	0.12-2.42	0.076	0.16	-0.98-1.31	0.78	-1.2	-0.002-2.57	0.05
	NHB	-0.1	-1.2-1.5	0.88	0.62	-0.78-2.02	0.39	0.46	-2.7-1.77	0.69
	NH-other	n/a			n/a			n/a		
	Unknown	-0.6	-0.72-0.52	0.44	0.11	-1.46-1.68	0.89	-1.22	-0.45-2.89	0.15
Payer	Medicaid									
	Private	-1.32	-2.36- -0.29	0.01	-0.68	-1.7-0.34	0.19	1.35	0.14-2.57	0.03
	Other	1.03	-3.28-1.22	0.37	1.39	-0.38-3.15	0.12	0.51	-1.26-2.28	0.57
Age (years)	<3									
	>3	-1.37	-2.37 - -0.375	0.007	-0.63	-1.57-0.31	0.18	-0.1	-1.05-1.14	0.93
MYCN amplification	Non-amplified									
	Amplified	1.32	0.32-2.32	0.009	1.39	0.36-2.42	0.008	0.16	-0.94-1.25	0.78
	Unknown	1.09	0.72-2.93	0.24	0.52	-1.35-2.4	0.54	-16	-4658-4625	0.99
Era of Diagnosis	2002-2008									
	2009-2015	-0.73	-1.65-0.19	0.12	-1.1	-2.1 - -0.12	0.027	0.32	-0.76-1.42	0.56
Line type	Totally implantable									
	External (PICC, DL tunneled or phoresis) *	0.91	-0.12-1.96	0.09	2.13	0.57-3.67	0.007	-1.19	-2.76-0.38	0.14
Received TPN	No									
	Yes	0.81	-0.18-1.81	0.112	1.002	0.21-1.98	0.045	0.66	-0.58-1.89	0.29

* refers to patient having external line at any point in induction therapy

refers to patient having external line at any point in induction therapy

Abbreviations: RR: Relative risk; DL: double lumen; NHW: Non-Hispanic White; HW: Hispanic White; NHB: Non-Hispanic Black; NH-other: Non-Hispanic Other; PICC: Peripherally-inserted central catheter; TPN: Total parenteral nutrition

TABLE 4
Multiple logistic regression analysis for all infections, blood stream infections only, and febrile neutropenia

		All infections			Blood Stream Infection			Febrile Neutropenia		
		RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
Sex	Male									
	Female	1.7	0.37–3.05	0.012	0.5	–0.6–1.7	0.36	–1.4	–2.8–0.01	0.05
	NHW									
	HW	0.08	–1.69–1.86	0.93	–0.5	–2.1–1.1	0.6	–1.4	–3.1–0.4	0.13
Race/Ethnicity	NHB	–1.07	–3.06–0.91	0.29	–0.1	–1.9–1.8	0.9	0.5	–2.0–3.0	0.70
	NH-other	n/a			n/a			n/a		
	Unknown	–1.4	–3.6–0.84	0.22	0.2	–1.8–2.2	0.9	–1.4	–3.5–0.7	0.20
	Medicaid									
Payer	Private	–1.8	–3.27–0.34	0.016	–1.1	–2.5–0.24	0.1	1.1	–0.4–2.6	0.15
	Other	0.6	–2.3–0.3	0.69	0.8	–1.4–2.9	0.5	0.9	–1.5–3.2	0.47
	<3									
Age	>3	–1.1	–2.4–3.5	0.14	–0.1	–1.3–1.1	0.9	–0.6	–2.0–0.8	0.38
	Non-amplified									
MYCN amplification	Amplified	1.4	0.01–2.76	0.05	1.3	0.6–2.5	0.04	0.05	–1.4–1.3	0.95
	Unknown	1.8	–0.38–4.02	0.11	0.9	–1.3–3.2	0.4	15.8	–4608–4640	0.99
	2002–2008									
Era of Diagnosis	2009–2015	0.1	–1.45–1.64	0.9	0.1	–1.3–1.5	0.9	–0.7	–2.4–0.9	0.38
	Totally implantable									
Line type	External (PICC, DL tunneled or phoresis) *	0.7	–1.13–2.52	0.5	1.8	–0.2–3.8	0.07	–2.6	–4.9–0.3	0.03

* refers to patient having external line at any point in induction therapy

refers to patient having external line at any point in induction therapy

Abbreviations: RR: Relative risk; DL: double lumen; NHW: Non-Hispanic White; HW: Hispanic White; NHB: Non-Hispanic Black; NH-other: Non-Hispanic Other; PICC: Peripherally-inserted central catheter; TPN: Total parenteral nutrition