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ORIGINAL ARTICLE

Perforations associated with peripherally inserted central catheters in a neonatal population

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Abstract
Background Peripherally inserted central catheters (PICCs) are increasingly used in neonates but perforations can result in devastating complications such as pericardial and pleural effusions. Identifying risk factors may guide surveillance and reduce morbidity and mortality.
Objective To determine the risk factors for PICC perforation in neonates.
Materials and methods Retrospective *case:control* (1:2) study of neonates admitted between 2004-2014. Charts and imaging were reviewed for clinical and therapeutic risk factors.
Results Among 3,454 PICCs, 15 *cases* of perforation (incidence 0.4%, 5 pericardial effusions, 10 pleural effusions) were matched to 30 *controls*, based on gestation and insertion date. Timing of perforations post-insertion was median 4 days for pericardial effusions and 21.5 days for pleural effusions. A risk factor for pericardial effusion was lower weight at PICC insertion compared with *controls*. There were no statistically significant differences between *cases* and *controls* in catheter material, insertion site, PICC size and lumen number. Among upper limb PICCs, pericardial effusions were associated with tip positions more proximal to the heart at insertion (P=0.005) and at perforation (P=0.008), compared with *controls*. Pleural effusions were associated with tip positions more distal from the heart at perforation (P=0.008). Within 48 h before perforation, high/medium risk infusions included total parenteral nutrition (100% *cases* vs. 56.7% *controls*, P=0.002) and vancomycin (60% *cases* vs. 23.3% *controls*, P=0.02).
Conclusion PICC-associated pericardial effusions and pleural effusions are rare but inherent risks and can occur at any time after insertion. Risk factors and etiologies are multifactorial, but PICC tip position may be a modifiable risk factor. To mitigate this risk, we have developed and disseminated guidelines for target PICC positions and routinely do radiographs to monitor PICCs for migration and malposition in our NICU. The increased knowledge of risk profiles from this study has helped focus surveillance efforts and facilitate early recognition and treatment.

Keywords Neonate · Perforation · Peripherally inserted central catheter · Radiography · Risk factors

Introduction

Peripherally inserted central catheters (PICCs) are fine, pliable catheters placed through a peripheral vein with the tip lying in a central vein (e.g., superior vena cava [SVC]). PICCs are increasingly used for central access in neonates and are considered to be a less-invasive alternative to the traditional central venous access devices [1, 2].

While PICCs are generally considered safe, outcomes associated with recognized complications range from no clinical impact to life-threatening events. Common examples of PICC complications are infection, thrombosis, migration, catheter embolism, catheter occlusion, endocarditis, and venous or cardiac perforation [3–9]. Premature infants have fragile tissues,

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which make them more susceptible to perforations from a PICC or central line and, although rare, life-threatening pleural and/or pericardial effusions [6, 7, 10, 11]. The etiology of perforations associated with PICCs is not well understood because frequently the PICC is not documented within the pericardial sac or pleural space. Suggested causes include trauma during the use of a wire, osmotic injury due to the infusion of hyperosmolar fluids, myocardial damage with thrombus formation, and rapid infusion rates of intravenous solutions [12]. Other risk factors include but are not limited to the position of the catheter tip, the material and size of the catheter, and the size or age of the patient [13, 14].

The purpose of this study was to review cases of perforations associated with PICCs in the neonatal intensive care unit (NICU) population to identify risk factors and guide surveillance for the highest risk infants.

Materials and methods

Research ethics approval was obtained from the hospital institutional review board. This was a retrospective, case-control study of infants admitted to the NICU at the Hospital for Sick Children, which is a quaternary NICU, based at a children's hospital between January 2004 and August 2014. The NICU has approximately 800 admissions annually. There are no deliveries on-site, and 30% of admissions have a primary diagnosis of a surgical condition.

Practice

PICCs were initially attempted at the bedside by the nurse PICC team in the NICU, as is our practice. If insertion was unsuccessful, patients were referred to Interventional Radiology for PICC placement. Interventional Radiology PICC placement utilized ultrasound (US) for access and the Seldinger technique to guide catheter insertion and tip position. Approximately half of the neonatal PICCs were placed by the NICU nurse-led PICC team and performed within that unit, and the remaining half were placed by the Interventional Radiology team and performed in that department.

PICC tip positions in the NICU were confirmed by radiographs immediately after the procedure before securement. Those noted to be malpositioned on the insertion radiograph were adjusted. This occurred in approximately 50% of insertions. If a PICC tip position was recognized as too distal, it was usually removed or replaced within a few days of insertion. NICU PICCs were secured by dressings and not sutured. In Interventional Radiology, PICC tip positions were confirmed by fluoroscopy during the procedure and at the conclusion of the procedure. Those PICCs were secured by a dressing and not sutured; if the PICC line was cuffed, a suture was placed at the skin adjacent to the line to make the incision snug around the cuff. During the study period, there was no formal protocol for arm or shoulder position for the radiographs. The majority of lower extremity PICCs were inserted in the NICU. Selection of silicone versus polyurethane catheters was based on availability of the catheters that were of a suitable size for each patient.

Data

Cases of PICC perforation were identified by reviewing the records of Morbidity and Mortality Rounds from both the NICU and the Interventional Radiology departments, and using an in-house radiology report word search engine. *Cases* included patients admitted to the NICU who had PICCs inserted by either the NICU team or the Interventional Radiology team and who developed a perforation. Data sources included the electronic medical records and the Picture Archive Communication System (PACS). Data elements analyzed included patient demographics such as birth weight and weight at the time of the PICC insertion, type of catheter inserted (material, French size, number of lumens), vein accessed, position of the PICC tip at insertion and on the day of the perforation, number of dwell days to perforation, nature of pleural or pericardial effusions, other PICC-related complications, and patient outcome. Infusates administered through the PICC in the 48 h preceding the perforation were categorised using established criteria of risk for extravasation (as high, intermediate or low) on the basis of four recognized biological and physical factors: extreme pH (less than 5 or greater than 9), osmolality, vasoactivity and cytotoxicity [15]. PICC tip position was determined by review of available imaging by two authors (A.J.S., a medical student, and B.L.C., with 22 years of experience) and was recorded in thoracic vertebral unit levels (or equivalent) with the following clarifications: a lower extremity PICC with a tip at the second lumbar vertebrae unit (L2) was reported as thoracic level T14 and a PICC with a tip in the subclavian vein was reported as T1. The appropriate PICC tip position in our institution was defined as in the region of the SVC/right atrium junction for upper extremity or scalp PICCs, and inferior vena cava (IVC)/right atrium junction for leg PICCs [16, 17]. The target tip position for upper extremity PICCs was between the carina and two vertebral units below the carina. The target tip position for lower extremity PICCs was at the IVC/right atrium junction and not necessarily dictated by vertebral unit level. For analysis, *cases* were subgrouped into perforations resulting in pericardial or pleural effusions. The term "proximal" was used to describe a position closer to the heart, and "distal" when further away from the heart.

Case: Control

A 1:2 case to control ratio was employed to identify risk factors for perforation. *Controls* were matched to *cases* by

gestational age and date of insertion. A priori, this matching design was chosen because gestational age was considered the most important factor to control since it is an accepted major risk factor. Date of insertion was chosen to avoid any potential effects from changes in clinical practices during the study period, which may not be measurable but could affect outcomes. Matching or controlling for other potential risk factors was deliberately avoided so risk factors could be identified in the *case:control* comparative analysis.

Controls were identified through the Vascular Access Database. The day of perforation post-PICC insertion for *cases* was used for the matched *controls* to collect data on PICC tip position and infusions administered so that the duration of PICC for these risk factors would be comparable for *cases* and *controls*.

Statistics

Baseline characteristics and outcomes were compared between the *case* and *control* groups using chi-square or Mann-Whitney *U* tests as appropriate. Odds ratios (OR) with their 95% confidence intervals were reported for proportions. A two-sided *P*-value of <0.05 was considered statistically significant. Data were analyzed using SPSS Version 22.0 (IBM Corp., Armonk, NY).

Results

During the almost 11-year period, 3,454 PICCs were inserted. Fifteen *cases* of perforation associated with PICCs were identified giving an incidence of 0.43%. Fourteen perforations (10 pleural effusions and 4 pericardial effusions) occurred with upper extremity PICCs and one pericardial effusion occurred with a lower extremity PICC. Eleven *cases* (seven pleural effusions and four pericardial effusions) were suspected clinically, three *cases* (two pleural effusions and one pericardial effusion) were detected incidentally, i.e. during imaging for underlying conditions or routine surveillance of PICC position, and one pleural effusion was found at autopsy (see below).

Ten perforations resulted in a pleural effusion (incidence of 0.29%) including one case that also had subcutaneous chest wall edema, and 5 perforations resulted in a pericardial effusion (incidence of 0.14%). Pericardial effusions occurred at a median (min, interquartile range [IQR], max) of 4.0 (1, 2, 6, 7) days post-PICC insertion, while pleural effusions occurred later at 21.5 (1, 4, 31, 40) days post-PICC insertion. Nine *cases* (six pleural effusions and three pericardial effusions) had drainage or aspiration of fluid, and the fluid analysis was consistent with total parenteral nutrition (elevated glucose and triglycerides). The median volume of fluid drained from the pleural effusions was 44 ml (*n*=6; range: 27-110 ml; mean: 55 ml). The median volume of fluid drained from pericardial effusion was 9 ml (*n*=3; range: 5-9 ml, mean: 8 ml). Five *cases* did not undergo percutaneous aspiration, but these effusions were attributed to PICC perforation by aspiration of total parenteral nutrition during PICC removal (*n*=1), or resolution of effusion with removal of the line in conjunction with abnormal line position as seen on chest radiograph (*n*=4). The remaining pleural effusion was noted at the time of autopsy. PICCs were managed by removing the catheter in 12 *cases*, pulling back the catheter in 2 *cases* and one had the PICC in situ at the time of death. Radiographs from two of the cases are shown in Fig. 1 (pleural effusion from a malpositioned PICC) and Fig. 2 (pericardial effusion from a malpositioned PICC).

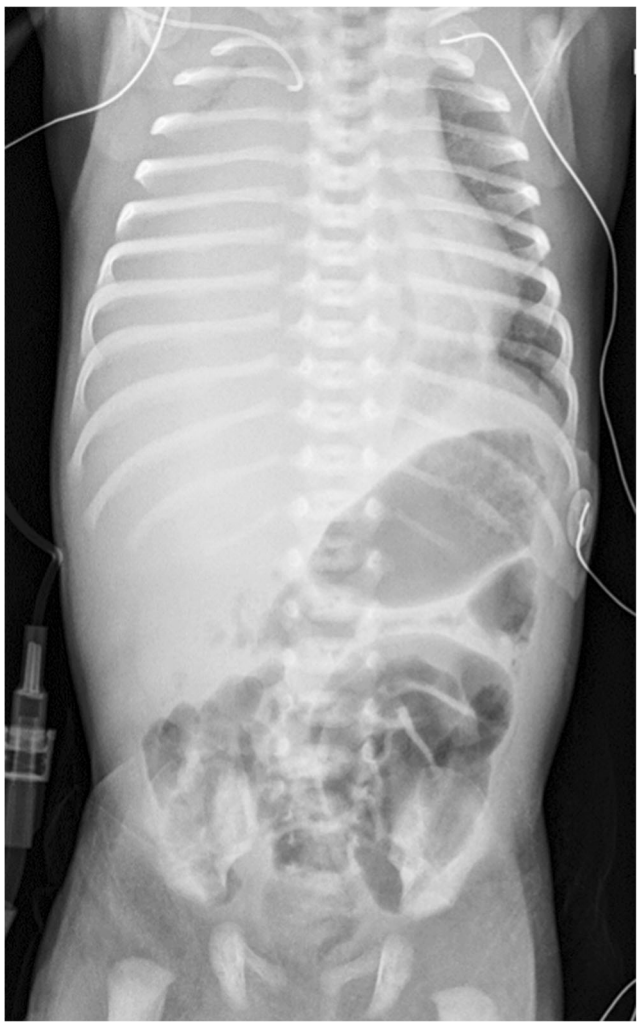

Fig. 1 Supine radiograph of a 17-day-old boy, born at 36 weeks' gestational age weighing 2,350 g. There is a right upper extremity peripherally inserted central catheter (PICC) in situ, with the tip curled infero-laterally at the level of the second thoracic vertebrae (T2). There is associated whiteout of the right side of the chest with slight mediastinal shift, consistent with a large right-side pleural effusion. Lateral view (not shown) confirmed PICC was curled anteriorly. Pleural fluid analysis confirmed total parenteral nutrition

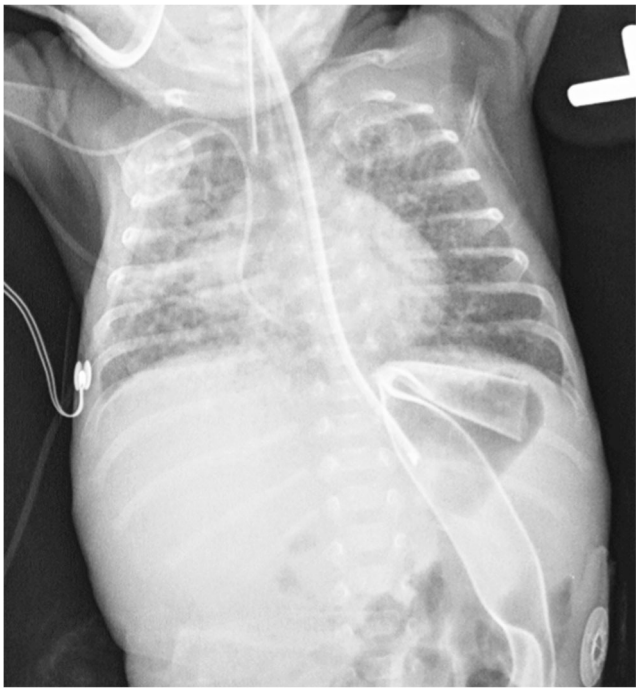

Fig. 2 Supine radiograph of a 2-week-old girl, born at 24 weeks' gestational age weighing 730 g, with intestinal perforation. A radiograph shows the patient intubated, with the nasogastric tube in situ, and a left-side surgical drain in left upper abdomen. There is a right upper extremity peripherally inserted central catheter in situ, with its tip projected over the inferior margin of T7, curved medially, and with associated cardiomegaly, before it was pulled back to T5-6 level (not shown). Nine milliliters of pericardial fluid were aspirated from the pericardium

Table 1 shows the patient demographics and comparison of all 15 *cases* subgrouped into pericardial effusion (*n*=5) or pleural effusion (*n*=10) compared with 30 *controls*. There were no significant differences in the matched variable of gestational age.

Cases with pericardial effusion were more likely to be female patients with lower weight at PICC insertion compared with *controls*. Table 2 demonstrates the assessment of possible risk factors for perforation. There were no statistically significant differences between *cases* and *controls* for the department inserting the line (Interventional Radiology vs. NICU), catheter material (polyurethane vs. silicone), site of insertion, right- or left-side approach, PICC size, and number of lumens. The PICC tip position at insertion and time of perforation for *cases* and *controls* are shown in Fig. 3 (upper extremity PICCs) and Fig. 4 (lower extremity PICCs). The median tip position migrated distally from the heart for both upper and lower extremity PICCs over time. *Cases* with pericardial effusion occurred with tip positions more proximal to the heart than in *controls*, both at insertion (*P*=0.005) and at the time of perforation (*P*=0.008) (Fig. 3), including one lower extremity PICC that was at T5.5 at the time of perforation 4 days after insertion (Table 2). Pleural effusion *cases* were associated with tip positions more distal to the heart at the time of perforation than *controls* (*P*=0.008). The bowed catheter sign was seen in two *cases* and one *control* [18]. Although there was a trend for perforations to be more commonly associated with polyurethane PICCs (93% of *cases*), this did not reach statistical significance.

The most commonly used high and medium risk infusates administered through the PICC in the 48 h preceding the perforation are shown in Table 2. Vancomycin and total parenteral nutrition were more likely to have been administered among *cases*. All *cases* were on total parenteral nutrition, at a median flow rate of 117 ml/kg/day or 6.8 ml/h. There was no significant difference in total parenteral nutrition flow rates between *cases* and *controls*.

There were no significant differences in mortality among *cases* (*n*=2) and *controls* (*n*=3). None of the deaths was directly related to the PICC. Among the *cases*, one patient with trisomy 21, renal failure and severe congenital heart disease died from septic shock following surgery for bowel perforation due to necrotizing enterocolitis. The death occurred 19 days post PICC insertion, and 1 day after the PICC was removed when total parenteral nutrition leakage was identified around an ipsilateral temporary internal jugular line. The second death occurred in a 24-week infant, at 56 days of age, and 29 days post PICC insertion. This patient, who had major complications of severe prematurity, had an acute deterioration with suspected septic shock. An autopsy found, in addition to the multi-organ sequelae of prematurity and meconium peritonitis, pleural effusions and signs of acute suppurative mediastinitis, which were attributed to perforation by the PICC. There were 3 deaths among the *controls*, the first from cardiorespiratory failure due to sepsis (99 days post PICC insertion), the second due to respiratory failure due to hydrops and hydrothorax (7 days post PICC insertion), and the third from an underlying CHARGE (coloboma, heart defects, choanal atresia, retardation of growth/development, genital anomalies, ear anomalies) syndrome (4 days post PICC insertion).

Discussion

Our study suggests that the profile of an infant at risk for a pericardial perforation is a small baby (median gestational age: 26 weeks; median birth weight: 1,080 g) with a PICC tip position more proximal to the heart, on total parenteral nutrition during the first week after PICC insertion (median: 4 days, range: 1–7 days). The profile of an infant at risk for a pleural perforation is a larger baby with a PICC tip position more distal from the heart, on total parenteral nutrition, at any time after PICC insertion (median: 21.5 days, range: 1 to 40 days).

The incidence of PICC-associated perforations in this cohort was 0.43% with subgroup rates of pericardial effusion of 0.14% and pleural effusion of 0.29%. A similar incidence of

Table 1 Demographics of cases with pericardial or pleural effusion compared with controls

	Controls *n*=30	Cases of Pericardial effusion or pleural effusion *n*=15	Cases to controls *P*-value OR (95% CI)*	Pericardial effusion *n*=5	Pericardial effusion vs. controls *P*-value OR (95% CI)*	Pleural effusion *n*=10	Pleural effusion vs. controls *P*-value OR (95% CI)*
Gender female; *n* (%)	15 (50)	9 (60)	0.53 1.50 (0.43, 5.27)	5 (100)	**0.04**	4 (40)	0.58 0.67 (0.16, 2.85)
Gestational age in weeks Median (min, IQR, max)	33.5 (24, 25, 35, 40)	33.0 (24, 25, 35, 40)	0.94	26.0 (24, 24, 30, 33)	0.13	35.0 (24, 28, 36, 40)	0.36
Birth weight in grams Median (min, IQR, max)	1,723 (580, 828, 2622, 3200)	1,080 (525, 800, 2340, 3400)	0.52	914 (730, 765, 1065, 1079)	0.13	1,920 (525, 982, 2472, 3400)	0.87
Weight at insertion in grams Median (min, IQR, max)	1,926 (715, 948, 2762, 3620)	1,250 (655, 822, 2410, 3430)	0.28	822 (689, 754, 1208, 1290)	**0.03**	1,962 (655, 931, 2536, 3430)	0.99
Primary diagnosis on admission; *n* (%)			0.74		0.06		0.68
Prematurity </=28 weeks	13 (43.3)	8 (53.3)		5 (100)		3 (30.0)	
Medical	9 (30.0)	3 (20.0)		0		3 (30.0)	
Surgical	8 (26.7)	4 (26.7)		0		4 (40.0)	
Age at PICC insertion in days Median (min, IQR, max)	8.5 (0, 4, 11, 85)	5.0 (2, 3, 9, 27)	0.10	5.0 (2, 3, 10, 12)	0.26	5.5 (2, 3, 10, 27)	0.17
Age at perforation in days Median (min, IQR, max)	Not applicable	15.0 (3, 6, 37, 56)	-	9.0 (5, 6, 14, 15)	-	25.5 (3, 10, 42, 56)	-
PICC dwell time prior to perforation in days Median (min, IQR, max)	Not applicable	7.0 (1, 3, 25, 40)	-	4.0 (1, 2, 6, 7)	-	21.5 (1, 4, 31, 40)	-
Mortality; *n* (%)	3 (10.0)	2 (13.3)	0.74 1.38 (0.21, 9.33)	0	0.46	2 (20.0)	0.41 2.25 (0.32, 5.90)

P-values in bold were statistically significant (<0.05)

CI confidence interval, *IQR* interquartile range, *max* maximum, *min* minimum, *PICC* peripherally inserted central catheter

*Odds ratio (OR) for proportions only, not calculable if event rate zero in either group

Table 2 Risk factors for cases with pericardial or pleural effusion compared with controls

	Controls *n*=30	All cases (pericardial effusion or pleural effusion) *n*=15	Cases to controls *P*-value OR (95% CI)*	Pericardial effusion *n*=5	Pericardial effusion vs. Controls *P*-value OR (95% CI)	Pleural effusion *n*=10	Pleural effusion vs. controls *P*-value OR (95% CI)
Insertion by: IR (vs. NICU); *n* (%)	14 (47)	9 (60)	0.40 1.71 (0.49, 6.03)	3 (60)	0.58 1.71 (0.25, 11.78)	6 (60)	0.46 1.71 (0.40, 7.34)
Site: Right (vs. left); *n* (%)	21 (70)	11 (73)	0.82 0.85 (0.21, 3.39)	3 (60)	0.66 1.56 (0.22, 10.96)	8 (80)	0.54 0.58 (0.10, 3.31)
Site: upper extremity (vs. lower extremity); *n* (%)	24 (80)	14 (93)	0.24 0.29 (0.03, 2.62)	4 (80)	1.00 1.0 (0.09, 10.66)	10 (100)	0.12
Vein accessed; *n* (%)			0.55		0.67		0.41
Basilic/brachial	17 (57)	11 (73)		4 (80)		7 (70)	
Cephalic	6 (20)	3 (20)		0		3 (30)	
Saphenous/femoral	6 (20)	1 (7)		1 (20)		0	
Scalp	1 (3)	0		0		0	
PICC							
Material: polyurethane (vs. silicone); *n* (%)	22 (73)	14 (93)	0.11 5.09 (0.57, 45.22)	5 (100)	0.19	9 (90)	0.27 3.27 (0.36, 30.10)
French size: 1.9 or 2.0 (vs. ≥2.6); n (%)	17 (57)	9 (60)	0.83 1.15 (0.32, 4.04)	4 (80)	0.32 3.06 (0.30, 30.73)	5 (50)	0.71 0.76 (0.18, 3.21)
# Lumens: 1 (vs. 2); *n* (%)	26 (87)	14 (93)	0.50 2.15 (0.22, 21.18)	5 (100)	0.39	9 (90)	0.78 1.38 (0.14, 14.07)
Cuffed (vs. uncuffed); *n* (%)	11 (37)	4 (27)	0.50 0.63 (0.16, 2.46)	0	0.10	4 (40)	0.85 1.15 (0.27, 4.99)
Tip levels							
Upper extremity at insertion; ***n***=24 Median (min, IQR, max)	5.0 (1, 4, 6, 13)	5.0 (1, 4, 6, 7)	0.39	7.0 (6, 6.25, 7, 7)	**0.005**	5.0 (1, 4, 5, 6)	0.67
Upper extremity at perforation Median (min, IQR, max)	4.0 (1, 3, 6, 6)	3.0 (1, 2, 5, 7)	0.36	6.2 (6, 6, 7, 7)	**0.008**	2.0 (1, 1, 3, 5)	**0.008**
Lower extremity at insertion; *n*=6 Median (min, IQR, max)	10.8 (7, 8, 12, 15)	2.0 (2, 2, 2, 2)	0.29	2.0 (2, 2, 2, 2)	0.29	No cases with lower extremity PICCs	n/a
Lower extremity at perforation Median (min, IQR, max)	12.0 (7, 8, 15, 15)	5.5 (5.5, 5.5, 5.5, 5.5)	0.33	5.5 (5.5, 5.5, 5.5, 5.5)	0.33	No cases with lower extremity PICCs	n/a
Medications administered 48 h prior to perforation							

Table 2 (continued)

	Controls *n*=30	All cases (pericardial effusion or pleural effusion) *n*=15	Cases to controls *P*-value OR (95% CI)*	Pericardial effusion *n*=5	Pericardial effusion vs. Controls *P*-value OR (95% CI)	Pleural effusion *n*=10	Pleural effusion vs. controls *P*-value OR (95% CI)
Any high risk: *n* (%)	13 (43)	7 (47)	0.83 0.87 (0.25, 3.04)	3 (60)	0.49 0.51 (0.07, 3.51)	4 (40)	0.85 1.15 (0.27, 4.92)
Caffeine: *n* (%)	9 (30)	5 (33)	0.82 0.86 (0.23, 3.23)	3 (60)	0.19 0.29 (0.04, 2.01)	2 (20)	0.54 1.71 (0.30, 9.72)
Inotropes: *n* (%)	2 (7)	3 (20)	0.12 0.29 (0.04, 1.94)	1 (20)	0.32 0.29 (0.02, 3.92)	2 (20)	0.22 0.29 (0.04, 2.36)
Acyclovir: *n* (%)	2 (7)	0	0.31	0	0.55	0	0.40
Vancomycin: *n* (%)	7 (23)	9 (60)	**0.02** 0.20 (0.05, 0.77)	3 (60)	0.09 0.20 (0.03, 1.47)	6 (60)	**0.03** 0.20 (0.04, 0.93)
TPN 48 h prior to perforation							
TPN: yes/no; *n* (%)	17 (57)	15 (100)	**0.002**	5 (100)	0.06	10 (100)	**0.01**
If Yes: TPN flow rate ml/kg/day; Median (min, IQR, max)	117 (67, 96, 136, 151)	115 (34, 59, 129, 151)	0.28	118 (102, 108, 130, 130)	0.631	77.5 (34, 51, 125, 151)	0.32
If Yes: TPN flow rate ml/h; Median (min, IQR, max)	6.8 (3, 4, 12, 18)	5.8 (3, 4, 10, 18)	0.22	4.6 (4, 4, 5, 6)	0.909	6.5 (3, 4, 11, 18)	0.29

P-values in bold were statistically significant (<0.05)

CI confidence interval, *IQR interquartile range, IR* interventional radiology, *max* maximum, *min* minimum, *NICU* neonatal intensive care unit, *PICC* peripherally inserted central catheter, *TPN* total parenteral nutrition

*OR (odds ratio) for proportions only, not calculable if event rate zero in either group

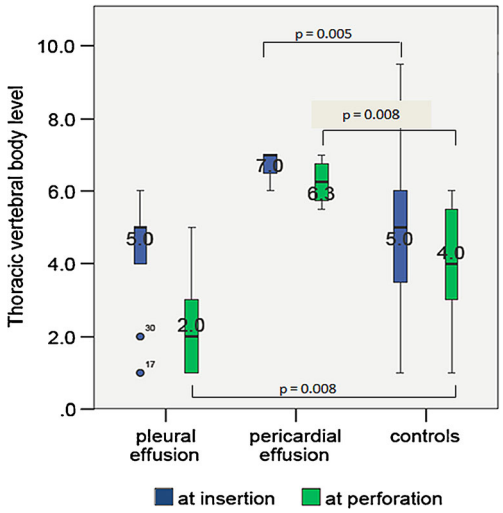

Fig. 3 Peripherally inserted central catheter (PICC) tip position at insertion and the time of perforation for cases and controls for upper extremity PICCs. *P*-values are shown for comparisons that have significant *P*-values. All other comparisons have *P*-values >0.05

0.3% to 2% is reported in the literature, but varied depending on the population, type of complication (pericardial or pleural effusion) and the study design [1, 2, 6, 19–21]. Beardsall et al. [6] in 2003 reported an incidence of 0.18% for pericardial effusion/tamponade in a survey to neonatologists based on self-reporting among 46,000 lines placed, acknowledging that this might be underreporting of rates. An incidence of 0.3% was reported for cardiac tamponade among 592 central venous catheters in neonates [20]. Cartwright et al. [21] examined all neonatal cases (2,186 catheters, 1,862 neonates) with central venous lines from 1984 to 2002, including autopsy reports in 89 cases, and found rates of pericardial effusion of 0.05% of catheters. Among very low birth weight infants, the

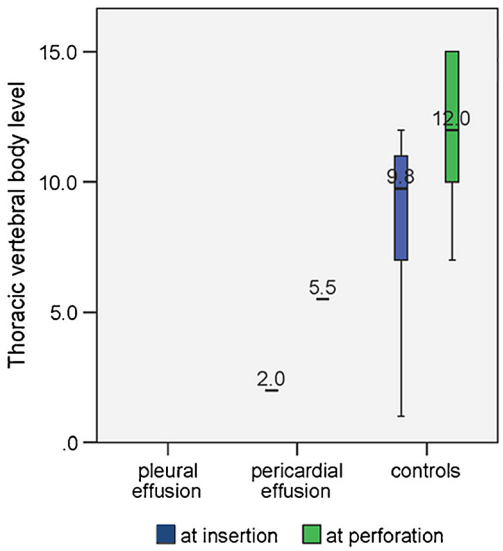

Fig. 4 Peripherally inserted central catheter (PICC) tip position at insertion and time of perforation for cases and controls for lower extremity PICCs. None of the comparisons has *P*-values <0.05

reported incidence is higher at 1.8-3% [19, 22]. With respect to pleural effusions, there are occasional reports in the literature, with incidences ranging from 0% to 2.2% [21, 23]. In a review of pleural effusions in 82 infants in a Level III NICU, 13 (20%) were ascribed to total parenteral nutrition extravasation [24]. Four unusual cases of pleural effusions have been reported in preterm infants secondary to migration of lines into the pulmonary artery, pulmonary vein and an umbilical venous catheter into the right atrium [23, 25].

The pathogenesis of PICC-related pleural or pericardial effusions remains debatable. Recognised causes include perforation through the vascular wall, trauma at the time of insertion, repetitive tapping on the vascular wall, hyperosmolarity of infusates, fragility of cardiac/vein wall, and adhesive thrombus. A combination or continuum of these events is likely [11, 12]. Perforation does not usually occur at the time of line insertion, as reflected in the later timing of presentation and lack of blood in the effusion. Pericardial effusions tended to occur within a few days after line insertion in the very small infants, suggesting fragility of the cardiac and vein wall is pertinent, given that *cases* of pericardial effusion were smaller and of lower gestational age than pleural effusion *cases* or *controls*. The lateral wall of the SVC is considered by some to be more fragile than the medial wall, so erosion from a line abutting the lateral wall or creating an acute angle poses an increased potential risk [2, 12–14]. Erosion of the vascular wall may occur from a jet effect, or the nature of the infusate, without any prior trauma [2]. The rates of infusions among *cases* and *controls* in this cohort were similar, and within standard rates for neonates. Hyperosmolarity of the infusates is a recognised cause of endothelial damage and tissue necrosis. In our series, we found a significant difference between *cases* and *controls* for those receiving at-risk infusions and vancomycin (classified as a medium risk drug), and all *cases* were on total parenteral nutrition, as reported by others [11, 15, 22].

With respect to clinical presentation, pericardial effusions occurred earlier (median: 4 days after PICC insertion) than pleural effusions (median: 21.5 days). Similar timing of pericardial effusion at 3 days after PICC insertion has been reported by others [19, 26]. Timing of pleural effusions has been shown to occur within a wider range of time (e.g., day 7-23 of life), similar to our findings (3-56 days of age; 1-40 days post insertion) [24, 25, 27]. In one series, the clinical presentation of 61 patients with pericardial effusion and tamponade was of acute collapse in two-thirds and unexplained instability in one-third [11]. Presentation of pleural effusion is usually less catastrophic and easier to manage than pericardial effusions. Among our *cases*, 1/5 (20%) of those with pericardial effusion and 2/10 (20%) of those with pleural effusion presented subclinically. This high rate of detection of subclinical *cases* for both

pericardial effusions and pleural effusions provide support for heightened surveillance efforts in neonates with PICCs.

We found that PICC tip position both at the time of insertion and at the time of perforation was a significant risk factor for perforation that may be modifiable and supports the need for ongoing close surveillance of PICC tip positions. Additionally, we found that PICCs migrated to a position more distal from the heart over time in both *cases* and *controls*. The reason for outward migration of lines was not clear but line migration after insertion has been described by others [28]. Possible mechanisms include loosening of the dressing, movement of the PICC during dressing changes, and growth of the baby. Among *cases* with pleural effusion, some PICCs migrated from a satisfactory position at the time of insertion to an unsatisfactory position. The median level of the tip of upper extremity PICCs at the time of perforation was more distal from the heart for pleural effusion *cases* (T2) compared with *controls* (T4) and more proximal to the heart for pericardial effusion *cases* (T6.2 for upper extremity and T5.5 for lower extremity PICCs) compared with *controls* (T4 for upper extremity and T12 for lower extremity). The literature suggests that the tip of a PICC should be in the region of the SVC/right atrium confluence, but not within the right atrium to avoid pericardial tamponade [7, 10, 11]. It has been advised to use the carina, which is usually located around T4, as a landmark rather than the cardiac silhouette [16]. In children, the SVC terminates two vertebral body units below the carina at approximately T6 [17, 29]. A PICC tip below the level of the pericardial sac may create conditions that increase the risk of pericardial perforation [2]. PICC tips more distal from the heart and cephalad to the carina are less likely to lead to conditions that cause pericardial effusion [16], but they are at increased risk of PICC migration and pleural effusions. Target triangles for positioning the tip of upper limb PICCs (1.7 vertebral body units below the carina) and lower limb PICCs (T9-11) have been graphically shown by the Cincinnati group, but do not avoid the risk of extravasation [30–32]. It is recognised that despite awareness of the risks inherent to different positions and all best efforts, ideal catheter tip location may be difficult to maintain [2, 19, 33]. Moreover, there are unavoidable ongoing changes in PICC tip position with arm movement, which may be inward or outward depending on the vein used, and position of the shoulder or elbow [7]. Gaballah et al. [34, 35] have demonstrated the usefulness of US for identifying and monitoring of tip positions in lower extremity PICCs. Thus, the emerging use of US for surveillance shows great promise in decreasing these complications. Routine US was not used for tip positioning in our cases, and only a minority of PICCs were in the lower extremity.

One of the strengths of our study was the use of a case-control design that allowed for assessment of risk factors for these rare events. Many risk factors were not modifiable, such as the gender, gestational age and weight of the baby. Even modifiable risk factors, such as choice of French size, material of PICC, number of lumens, and site of insertion and tip position, are not entirely within the control of the health care provider inserting the line, but are usually dictated by the clinical scenario [2]. Choice of site is largely determined by the availability of a suitable vein [1, 33]. One study of 626 lines in 559 neonates showed no significant difference in complication rates requiring PICC removal, between upper or lower extremity PICCs, although non-central tip positions were found more commonly in upper extremity PICCs [33]. The choice of infusions is determined by the clinical needs of the infant, which may also dictate the number of lumens and type of PICC required. Polyurethane is stronger and stiffer than silicone and enables a larger inner luminal diameter with a thinner wall, but it may be more prone to perforation. Some authors advocate choosing silicone lines, but perforations have been reported with both [11]. There was a trend for increased risk of perforation with polyurethane catheters, OR 5.09 (95% CI 0.57, 45.22; P=0.11) compared to silicone; however, this difference did not reach statistical significance. These results are limited due to the relatively infrequent use of silicone catheters in our cohort, as they were used in only 20% (n=9/45) of all patients.

Menon [2] addressed the overall safety of neonatal long lines, given their increasing use, their challenges and recognised risks, and advised a balanced approach with a risk-benefit assessment recognizing that for many neonates their PICC may represent a lifeline. It is recognized that a high level of suspicion is required for any infant who shows signs of instability or deterioration in the presence a central line [2, 11, 19, 22] as deaths have been reported due to delayed diagnosis and treatment. Early recognition and institution of management such as imaging to, discontinuation of infusion, reposition of PICC are essential [6, 11, 20, 22, 36]. Various guidelines have been developed that are aimed at optimizing recognition and treatment [22, 36]. Factors to be considered that may reduce the risk of morbidity or mortality from perforation include judicious consideration of whether and/or when to place a PICC, careful attention to tip position at insertion, and ongoing surveillance of tip positions over time for infants with the above risk profiles.

There are several limitations to this study. It was a retrospective review of patients from a single surgical quaternary NICU. The findings may not be directly applicable to different NICU populations. Due to the rarity of the cases, the sample size was limited and did not allow full assessment of potential risk factors. Some risk factors showed trends for differences between *cases* and *controls*, but did not attain statistical significance, possibly due to insufficient power. A larger number of controls may have increased the statistical power of the study. Small numbers also precluded multivariate analysis that

could have examined the relationships among multiple variables. Recording the tip position on radiographs had inherent errors due to angulation and parallax. These errors may be minimized when the tip position is measured relative to the carina rather than the vertebrae, as was used for this study [16]. The latter was used in our patients who underwent radiographs in the supine position with the X-ray tube perpendicular to the infant, as the vertebral bodies were more consistently seen than the carina when retrospectively reviewing stored low-dose fluoroscopic images.

Conclusion

Pericardial and pleural effusions associated with PICCs are a rare but inherent risk and can occur any time after insertion. Risk factors and etiologies are multifactorial, but PICC tip position may be a modifiable risk factor. To mitigate this risk, we have developed and disseminated guidelines for target PICC positions and routinely do radiographs to monitor PICCs for migration and malposition in our NICU. The increased knowledge of risk profiles from this study has helped focus surveillance efforts and facilitate early recognition and treatment.

Compliance with ethical standards

Conflicts of interest None

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