CATHETER RELATED BLOOD STREAM INFECTION IN A TERTIARY NEONATAL INTENSIVE CARE UNIT IN CAIRO; A PROSPECTIVE OBSERVATIONAL STUDY

By

Ghada A. Saleh[1]*, Rania I. H. Ismail[1]

[1]Pediatrics Departments, Faculty of Medicine, Ain Shams University, Cairo, Egypt

***Correspondence to:** Ghada Ahmad Saleh

Affiliation: Lecturer of Pediatrics, Department of Pediatrics, Faculty of Medicine, Ain Shams University

E-mail: Ghadasaleh@med.asu.edu.eg

Mobile no.: +20-1148777714

ABSTRACT

Background: *Although the use of central lines is mandatory in neonatal intensive care units (NICUs), it has multiple complications. Central line associated blood stream infection (CLABSI) is one of the major risk factors to blood stream infection, mortality, and prolonged hospital stay in neonatal population. While care bundles focus on lowering infection rate, quality improvement studies aim to minimize the use of central line.*

Aim of the work: *To evaluate the incidence of catheter related blood stream infection (CLABSI) in babies admitted to NICU of Children Hospital of Ain Shams University over a 6-month period (from 6/2021-12/2021).*

Subjects and Methods: *In this prospective observational study, all neonates who had their first central line inserted during the study period were enrolled regardless of their gestational age or diagnosis. Patients who had early onset neonatal sepsis or had their line removed within 48 hours were excluded. Data of line insertion was collected (e.g., cause of insertion, type of line, time of insertion), and line viability was checked daily (e.g., duration, line culture) till removal of the line or death of the baby.*

Results: *Data from 44 lines (5 Peripherally inserted central catheter PICCs, 18 umbilical catheters, 21 central venous catheters) was analyzed. The most common indication for central line insertion was critical condition (e.g., sever sepsis, post-operative). No statistical correlation between type of line and patient outcome, positive line culture, and central line duration ($p>0.05$). CLABSI rate was 55.5/1000 central line days. 75% of cultured lines were positive and 34 babies (77.2%) had at least one*

positive culture proven infection (central line or blood). Positive blood culture (not line culture) was significantly corelated to mortality (p=0.012& p=1.00). Klebsiella was the most identified organism either in the central line (10 cases) or in blood (13 cases). klebsiella in blood (not central line) was significantly correlated to increased mortality compared to other organisms (p=0.027, p=0.108 respectively).

Conclusion: *Our data suggest that positive blood culture particularly with Klebsiella might correlate with poorer outcome. While central line related infection rate was very high (75%), this might not alone correlate to mortality. Further controlled trials are recommended to estimate the exact impact of central line presence on neonatal outcome and length of stay.*

Key words: *CLABSI, PICC, CVC, Klebsiella.*

INTRODUCTION

The exact burden of neonatal infection in -low- & middle-income countries is hard to estimate and can vary between countries. Overall, rates of neonatal infections are 3-20 times higher in developing than developed countries. Klebsiella pneumoniae, other gram-negative rods (Escherichia coli, Pseudomonas, Acinetobacter), and Staphylococcus aureus are frequent pathogens identified **(Zaidi et al., 2015)**.

Central line (CL) is any line that terminates at or close to the heart or is in one of the great vessels **(CDC, 2017)**. The use of central lines is mandatory in neonatal intensive care units (NICUs); however, it has multiple complications. While some of these can be fatal, most of the complications can be avoided by proper education, auditing, and monitoring **(Duesing et al., 2016)**.

Central line associated blood stream infection (CLABSI) is "laboratory-confirmed bloodstream infection not related to an infection at another site that develops within 48 hours of a central line placement" **(CDC, 2017)**. It is one of the major risk factors to infection, mortality, poor neurodevelopmental outcome, and prolonged hospital stay in neonatal population. This sparked the efforts globally to intervene by multiple quality improvement programs and by introduction of central line care bundles that significantly decreased the rates of CLABSI **(Bierlaire et al., 2021)**.

While care bundles focus on following multiple steps during both CL insertion and maintenance to lower the incidence of infection, quality improvement studies aimed deeper, by trying to minimize the need for central line by promoting

early feeding, setting maximum duration for central line use, early removal and revising decision to keep the central line daily **(Mais et al., 2015)**.

Aims of the Work

To evaluate the incidence of catheter related blood stream infection in babies admitted to a tertiary NICU over a 6-month period from 06/2021-12/2021.

Sample size justification:

EpiInfo® version 6.0 program was used to calculate the sample size. Statistical calculator based on 95% confidence interval and power of the study 80% with α error 5% (at least 34 patients).

Ethical consideration:

1. An informed consent was obtained from parents or the legal guardians before enrollment in the study.
2. An approval by the local ethical committee was obtained before the study was conducted.
3. The authors declare no potential conflicts of interest with respect to the research authorship and\or publications of this article.
4. All data of the patients and results of the study are confidential, and patients have the right to keep it.
5. Authors received no financial support for research, authorship and\or publications of this article.

PATIENTS AND METHODS

Patients:

During the study period, babies were eligible for enrollment once the medical team decided they require a central venous line insertion for their first time for any reason, and regardless of their weight, gestational age, or diagnosis. Babies who had their central line removed within 48 hours from insertion, and those who had early onset sepsis were excluded.

Methods:

One line was counted and analyzed per patient (only the initial one). Investigators collected data of insertion and line follow up. Insertion data included patients' age at insertion, reason for line insertion, type of central line (Umbilical venous catheter (UVC), central venous catheter (CVC) or peripherally inserted central catheter (PICC)), time of insertion, position of tip of the catheter and any complication related to the procedure. Tip position was confirmed by plain Xray which was reviewed by senior staff member.

Daily follow up data was concerned with line viability till its removal. Data included total central line days, any further complications related to the line, culture proven blood or line infection, antibiotic coverage throughout the line duration, reason of central line removal and outcome of the baby.

Unit policy to detect infection:

On admission, all babies undergo sepsis screen, including blood culture, full blood count and C-reactive protein. This is repeated with every suspected episode of sepsis. On suspicion of central line infection, two blood cultures are sent (one peripheral and one from the line). All lines are sent to culture once removed whether line infection is suspected or not. Other cultures (e.g., urine, cerebrospinal fluid, etc.) are sent when local infection is suspected. Study end point was removal of central line for any cause or the death of the baby. The CLABSI rate is calculated per 1,000 central line-days by dividing the number of CLABSIs by the number of central line-days and multiplying the result by 1000 **(CDC, 2017)**.

Statistical Analysis

Data was collected, revised, coded, and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as median, inter-quartile range (IQR) with non-parametric data, and qualitative variables were presented as number and percentages.

The comparison between groups with qualitative data was done by using Chi-square test. Comparing two groups with quantitative data and non-parametric distribution was done by using Mann-Whitney test and more than two groups by Kruskall Wallis test. Kaplan-Meier analysis was used using log rank test to assess the relation between type of central line and outcome of the studied patients. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:

$P > 0.05$: Non-significant, $P < 0.05$: Significant and $P < 0.01$: Highly significant.

RESULTS

Over the 6-month study period, 46 babies had central line inserted for their first time (5 PICC lines, 19 UVCs and 22 CVCs). Two lines were excluded from the analysis due to major adverse event a**t**tributed directly to line insertion and requiring immediate line removal; one had UVC inserted in the umbilical artery causing unilateral limb ischemia; the other suffered profound desaturation during CVC faulty passage causing unilateral hemothorax.

Central line days and CLABSI rate were calculated from duration and number of positive cultures **(CDC, 2017)**. Central line days were 324 days during which all babies were covered by systemic broad-spectrum antibiotics. CLABSI rate was 55.5/1000 central line days. Only 54.5% (24/44) of the lines were cultured, of which, 18 came back positive (75%). Lines were not cultured due to death of the baby with line in situ or line can't be sent for culture (contaminated/ no longer sterile).

Table (1): Demographic and clinical data of studied patients at time of insertion

		Type of line			Total	P-value
		PICC	UVC	CVC		
		No. = 5	No. = 18	No. = 21		
Age	Median (IQR)	4 (3 - 14)	2 (1 - 4)	12 (6 - 21)	4.5 (2 - 13)	**0.000‡**
	Range	1 – 16	1 – 7	2 – 53	1 – 53	
Gender	Male	2 (40.0%)	10 (55.6%)	11 (52.4%)	23 (52.3%)	0.827*
	Female	3 (60.0%)	8 (44.4%)	10 (47.6%)	21 (47.7%)	
Site	Upper Limb	3 (60.0%)	0 (0.0%)	0 (0.0%)	3 (6.8%)	**0.000***
	Lower Limb	2 (40.0%)	0 (0.0%)	0 (0.0%)	2 (4.5%)	
	Umbilical cord	0 (0.0%)	18 (100.0%)	0 (0.0%)	18 (40.9%)	
	Internal Jugular vein	0 (0.0%)	0 (0.0%)	21 (100.0%)	21 (47.8%)	
Side	Right	2 (40.0%)	0 (0.0%)	18 (85.7%)	20 (45.6%)	0.000*
	Left	3 (60.0%)	0 (0.0%)	3 (14.3%)	6 (13.7%)	
	Umbilicus	0 (0.0%)	18 (100.0%)	0 (0.0%)	18 (40.9%)	
Tip position	Adequate	3 (60.0%)	13 (72.2%)	14 (70.0%)	30 (69.8%)	0.870*
	Inadequate	2 (40.0%)	5 (27.8%)	6 (30.0%)	13 (30.2%)	
Repositioned	Repositioned	1 (20.0%)	2 (11.1%)	1 (5.6%)	4 (9%)	0.608*
	Not repositioned	4 (80.0%)	16 (88.9%)	17 (94.4%)	40 (91%)	
Reason	Critical	2 (40.0%)	7 (38.9%)	9 (42.9%)	18 (40.9%)	0.013*
	Exchange	0 (0.0%)	4 (22.2%)	2 (9.5%)	6 (13.7%)	
	No access	0 (0.0%)	1 (5.6%)	9 (42.9%)	10 (22.7%)	
	Medical	3 (60.0%)	6 (33.3%)	1 (4.8%)	10 (22.7%)	

‡PICC: Peripherally inserted central catheter, UVC: umbilical venous catheter, CVC: central venous catheter

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

*:Chi-square test; ‡: Kruskal Wallis test

Table 1 shows that 23 males vs 21 females required central line insertion, with median patient age at insertion of 4.5 days. Two PICC lines were inserted in the lower limb and 3 in the upper limb. All the 21 CVCs were inserted in the internal jugular vein (18 Right, 3 left). Almost 60% of lines were inserted during the night shift. Only 4/13 lines that were observed to be not in an optimum position were repositioned (30%). The most common indication for central line insertion was high volume of infusions in critical patients (e.g., septic shock, postoperative care) (40%). Other causes were difficult or no peripheral access (22.7%), various medical causes necessitating central access (e.g., resistant hypoglycemia) while the least common cause was exchange transfusion (13.6%).

Table (2): Central line duration, cause of removal and culture results:

		Type of line			Total	P-value
		PICC	UVC	CVC		
		No. = 5	No. = 18	No. = 21		
Duration of line	Median (IQR)	5 (4 - 7)	6 (4 - 10)	7 (2 - 14)	6.5 (3 - 11)	0.880‡
	Range	3 – 21	2 – 14	1 – 22	1 – 22	
Cause of central line Removal	No further need	1 (20.0%)	7 (43.8%)	6 (30.0%)	14 (34.1%)	0.091*
	Accidentally removed	2 (40.0%)	1 (6.3%)	2 (10.0%)	5 (12.2%)	
	Death	2 (40.0%)	2 (12.5%)	9 (45.0%)	13 (31.7%)	
	Complicated line	0 (0.0%)	6 (37.5%)	3 (15.0%)	9 (22%)	
Central line culture	Negative	1 (100.0%)	2 (13.3%)	3 (37.5%)	6 (13.6%)	0.093*
	Positive	0 (0.0%)	13 (86.7%)	5 (62.5%)	18 (40.9%)	
Blood culture	Negative	1 (33.3%)	6 (50.0%)	8 (42.1%)	15 (34%)	0.843*
	Positive	2 (66.7%)	6 (50.0%)	11 (57.9%)	19 (66%)	

PICC: Peripherally inserted central catheter, UVC: umbilical venous catheter, CVC: central venous catheter

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

*:Chi-square test; ‡: Kruskal Wallis test

Table 2 presents the follow up data of the line. The overall median duration of central line was 6.5 days (3-11) and showed no statistical difference between the three types of line (p=0.880). 34/44 babies (77.2%) had at least one positive culture proven infection (central line or blood), 7 had all their cultures negative, and 3 had no results of any culture in their records. No significant correlation was

observed between the type of line and culture result (p<0.05).
As per the reason for line removal, 56.1 % of the lines were removed when line was no longer required, either due to improvement (34.1%) or death (31.7%) of the baby. Five lines were dislodged while 9 (22%) lines were intentionally removed due to complication (3/44 thrombosed, 5/44 infected, 1/44 migrated). No statistical differences were observed between the 3 types of lines regarding duration of line, central line or blood culture result, or reason for line removal (p>0.05).

Table (3): Patients' outcomes per type of line:

		Type			Total n (%)	P-value*
		PICC	UVC	CVC		
		No. = 5	No. = 18	No. = 21		
Patient outcome	Improved	3 (60.0%)	14 (77.8%)	9 (42.9%)	26 (59%)	0.204
	Died	2 (40.0%)	4 (22.2%)	10 (47.6%)	16 (36.5%)	
	Still admitted	0 (0.0%)	0 (0.0%)	2 (9.5%)	2 (4.5%)	

PICC: Peripherally inserted central catheter, UVC: umbilical venous catheter, CVC: central venous catheter
P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *:Chi-square test

Table 3 shows that the overall mortality was (36.4%). Mortality was highest among patients with CVC (47.6%) compared with those of PICC (40%) and UVC (22.2%). However, this didn't reach statistical significance (p=0.204).

Table (4): Correlation between outcome and culture results:

	Outcome				P-value*
	Alive		Died		
	No.	%	No.	%	
Positive central line culture	15	75	3	75	1.000
Positive blood culture	7	36.8%	12	80.0%	**0.012**

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *:Chi-square test

Table 4 shows that positive blood culture was significantly correlated to mortality (p=0.012). On the other hand, positive central line culture was not (p=1.00).

Table (5): Correlation between duration of line and outcome, reason for removal and a culture results:

		Duration of line Median (IQR)	P-value
Patient outcome	**Improved**	6 (4 – 9)	0.102‡‡
	Died	7 (2 – 11)	
	Still admitted	17.5 (17 – 18)	
Positive culture	**Positive central line culture**	7 (3 – 11)	0.815‡‡
	Positive blood culture	9 (4 – 14)	0.269‡‡
Reason for removal	**No further need**	7 (5 – 9)	0.194‡‡
	Dislodged	4 (4 – 17)	
	Death	5.5 (2 – 7.5)	
	Complicated	11 (6 – 14)	

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) ‡‡: Kruskal Wallis test

Table 5 shows that the central line duration was not statistically correlated with patient outcome, culture results or reason for line removal (p>0.05).

Table (6): Results of central line and blood cultures:

Variable	Central line culture		Blood culture	
	N	%	N	%
Negative	**6**	**25%**	**15**	**44.1%**
Total positive	**18**	**75%**	**19**	**55.9%**
Klebsiella only	5	20.8%	9	26.5%
Cons only	4	16.7%	4	11.8%
Klebsiella + Candida	2	8.3%	1	2.9%
Klebsiella + Pseudomonas	1	4.2%	0	0
Cons + Candida	1	4.2%	1	2.9%
Staph Eqidermidis	1	4.2%	0	0
Klebsiella + Cons	1	4.2%	0	0
Acinetobacter	1	4.2%	0	0
Enterococci + cons	1	4.2%	1	2.9%
Acinetobacter + klebsiella	1	4.2%	0	0
Klebsiella + E coli	0	0	3	8.8%

Table (7): Correlation between cultures positive for Klebsiella and patient outcome, type, and duration of line

			Negative culture	Klebsiella present	Any other organism	P-value*
			n %	n %	n %	
Central line	Type of line	Picc	1 (16.7%)	0 (0.0%)	0(0.0%)	0.308
		UVC	2 (33.3%)	7 (70.0%)	6(75.0%)	
		CVC	3 (50.0%)	3(30.0%)	2(25.0%)	
	Patient Outcome	Improved	4 (66.7%)	8(80.0%)	7(87.5%)	0.503
		Died	1 (16.7%)	2(20.0%)	1(12.5%)	
		Still admitted	1 (16.7%)	0(0.0%)	0(0.0%)	
	Duration of line	Median (IQR)	7 (4 - 14)	7 (5 - 11)	7.5 (3 - 13)	0.939
Blood culture	Type of line	Picc	1(6.7%)	2 (15.4%)	0 (0%)	0.666
		UVC	6 (40%)	3 (23.1%)	3 (50%)	
		CVC	8 (53.3)	8 (61.5%)	3 (50%)	
	Patient Outcome	Improved	12 (80%)	3 (23.1%)	2 (33.3%)	**0.027**
		Died	3 (20%)	9 (69.2%)	3 (50%)	
		Still admitted	0 (0%)	1 (7.7%)	1 (16.7)	
	Duration of line	Median (IQR)	6 (4 - 9)	10.5 (7 - 14.5)	4 (3 - 11)	0.108

Picc: Peripherally inserted central catheter, UVC: umbilical venous catheter, CVC: central venous catheter

P-value >0.05: Nonsignificant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

*: Chi-square test

Tables 6 &7 show that 19 babies (55.9%) had positive blood culture with at least one organism identified, while 15 babies had negative blood culture (44.1%). Ten babies had no available blood culture result. 75% of the cultured central lines came back positive.

Klebsiella was the most identified organism either in the central line (10/24 cultured lines) or blood culture (13/34 blood culture). Babies who had klebsiella (alone or with other organism) detected in their central line culture had no different outcome from those who had either negative culture or positive for organism other than klebsiella. (P value >0.05). On the other hand, the presence

of Klebsiella in the blood culture significantly increased the mortality but had no effect on central line duration (p=0.027, p=0.108 respectively).

Table (8) & Figure (1): Kaplan Meier survival analysis for relation between overall survival and type of line:

		Total no.	No. of events	Mean	SE	95% CI		Test value	P-value
						Lower	Upper		
Type of line	PICC	5	2	14.000	7.000	0.280	27.720	0.473	0.790
	UVC	17	4	11.241	1.049	9.185	13.296		
	CVC	20	9	13.185	2.081	9.106	17.264		

Picc: Peripherally inserted central catheter, UVC: umbilical venous catheter, CVC: central venous catheter
P-value >0.05: Non significant (NS), CI: confidence interval.

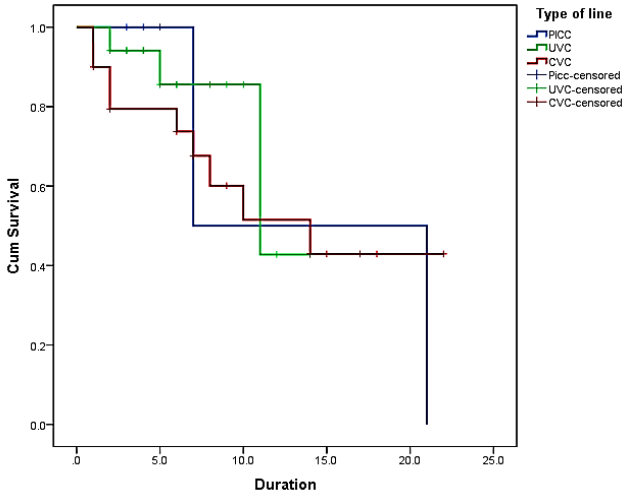

Figure (2): Kaplan Meier survival analysis

Table (8) & figure (1) illustrates that cumulative survival showed no statistical relation to type of line (p=0.102). This is shown by Kaplan Meier survival analysis above.

DISCUSSION

Our prospective observational study aimed to evaluate the central line related blood stream infection in babies admitted to NICU of Children hospital of Ain Shams university over a 6-month period (from 6/2021-12/2021). Patients were monitored and data of the central line was collected from the

point of insertion till the line removal.

In the current study, the median age of insertion was significantly higher in CVCs followed by PICC then UVC. This is explained by the characteristics of each line. UVC is usually inserted in the first few days of babies' lives while CVC is often preserved for older babies or those who have difficult access.

Remarkably, 100% of babies had their CVC inserted in the internal jugular vein which is the preferred site in the neonatal population because of the relative ease of insertion. However, line fixation and its presence in the neck might make it hard to maintain both its position and sterilization. In a large multi-center trial including 3000 adult patients with central line, **Parienti et al., 2015** reported that using the subclavian site for central venous catheterization reduced infections to a minimum but tripled the risk of pneumothorax compared to the internal jugular position. Moreover, **Yaseen at al., 2016** reported reduction in CLABSI rate from 2 to 0/1000 after shifting from internal jugular to subclavian approach as a part of care bundle. However, this was not studied in neonates.

In the current study, there was no statistical correlation between type of line and patient outcome, positive line culture, central line duration or any positive culture. Central line duration was also not statistically correlated with patient outcome, culture results and reason for line removal.

Similarly, in a study recruiting 120 neonates in a tertiary center in Egypt, **Rabie et al., 2022** reported different rate of central line infection among the three central line types. They reported 47.5 % in CVC, 35% in UVC and 22.5 % in PICC, however, this didn't reach statistical significance. Moreover, **Dubbink-Verheij et al., 2017** found no difference between the CLABSI incidence in CVCs, PICCs, and UVCs. In their study, occurrence of CLABSI was associated with parenteral nutrition, male gender, and higher birth weight.

In our study, and regarding antibiotics use, 100% of babies had all their central line days covered by broad spectrum antibiotics. While **Dubbink-Verheij et al., 2017** found that antibiotic treatment at birth was associated with a decreased risk of CLABSI, **Graus et al., 2022** concluded that prolonged use of antibiotics has been associated with increased mortality, major morbidities such as late onset

sepsis, necrotizing enterocolitis, bronchopulmonary dysplasia, and neurodevelopment impairment in very low birth weight (VLBW) infants. They also highlighted other consequences related to antibiotic overuse. This includes increased antimicrobial resistance, appearance of fungal infections and increased health care costs.

As per patient outcome, the current results showed no correlation between rate of CLABSI and neonatal outcome, with highest line infection rate in UVC (88.6%) but lowest mortality (22%) compared to CVC (62.5%, 47.6% respectively). This comes in line with **Różańska et al., 2015**, who conducted a large Polish study in 5 neonatal units involving 2003 VLBW babies. They found that general condition of the infants statistically increases both mortality and length of stay (LOS); while the presence of central line infection significantly prolonged LOS but not mortality, which was significantly higher in non-infected neonates.

Moreover, and in a recent nested case control study of 179 neonates, **Garcia et al., 2019** concluded that management of underlying diseases in specialized NICU contributes to a greater extent to the development of a central line-associated bloodstream infection more than the presence of the line itself.

Furthermore, **Goudie et al., 2014** estimated the attributable cost and hospital stay between matched CLABSI cases (1339) and non-CLABSI controls (2678) was $55,646 (2011 dollars/patient) and 19 days respectively. Along the same line, **Karagiannidou et al., 2020** in a systematic review assessing length of stay, cost, and mortality of healthcare-acquired bloodstream infections in children and neonates. They found the pooled attributable mortality rate was 8% (95% CI, 6–9) and LOS was 16.9 days compared to non-infected cases.

In our study, CLABSI rate was 55.5/1000 central line days, with 34 babies (77.2%) had at least one positive culture proven infection (central line or blood). Overall, the incidences of hospital acquired infections are higher in developing versus developed countries. In a review of literature, **Rosenthal, 2009** stated that CLABSI rates ranged from 2.6 to 60 cases per 1000 central line days in limited-resource countries compared with 0.8-2.9 cases per 1000 central line days in the USA with prevalence of gram-negative organisms.

In our study, Klebsiella was the most identified organism either in central line (10/24 cultured lines)

or blood cultures (13). Klebsiella in blood culture increased the risk of mortality but not the line duration and had no effect on both if present in central line. **Ghotaslou et al., in 2007** reported similar results; with Klebsiella being the most prevalent organism causing neonatal sepsis (31.43%) and with highest incidence of mortality. Moreover, **Hammoud et al., 2017** in a multi-center study in 3 countries in GULF region concluded that gram-negative organisms, particularly Klebsiella, were the commonest cause of late onset sepsis in neonatal population and were having high levels of resistance to third generation cephalosporins.

Study limitation:

The presence of matched control groups would have given another dimension to our study by comparing rates of infection in babies with or without central line. However, the main aim of the study was to estimate the burden of the central line within the babies with central line inserted.

CONCLUSION

Our data suggest that positive blood culture particularly with Klebsiella might correlate with poorer outcome. While central line related infection rate was very high (75%), this might not alone correlate to mortality. Further controlled trials are recommended to estimate the exact impact of central line presence on neonatal outcome and length of stay.

REFERENCES

1. **Bierlaire, S., Danhaive, O., Carkeek, K. and Piersigilli, F., (2021):** How to minimize central line–associated bloodstream infections in a neonatal intensive care unit: a quality improvement intervention based on a retrospective analysis and the adoption of an evidence-based bundle. European journal of pediatrics; 180 (2), pp.449-460.
2. **Centers for Disease Control and Prevention, (2017):** Bloodstream infection event (central line-associated bloodstream infection and non-central line-associated bloodstream infection). Device-associated Module BSI; pp.1-38.
3. **Dubbink-Verheij, G.H., Bekker, V., Pelsma, I.C., van Zwet, E.W., Smits-Wintjens, V.E., Steggerda, S.J., et al., (2017):** Bloodstream infection incidence of different central venous catheters in neonates: a descriptive cohort study. Frontiers in pediatrics; 5,

p.142.

4. **Duesing, L.A., Fawley, J.A. and Wagner, A.J., (2016):** Central venous access in the pediatric population with emphasis on complications and prevention strategies. Nutrition in Clinical Practice; 31(4), pp.490-501.
5. **Garcia, H., Romano-Carro, B., Miranda-Novales, G., González-Cabello, H.J. and Núñez-Enríquez, J.C., (2019):** Risk factors for central line-associated bloodstream infection in critically ill neonates. The Indian Journal of Pediatrics; 86(4), pp.340-346.
6. **Ghotaslou, R., Ghorashi, Z. and Nahaei, M., (2007):** Klebsiella pneumoniae In neonatal sepsis: a 3-year-study in the pediatric hospital of Tabriz Iran. Japanese journal of infectious diseases; 60(2/3), p.126.
7. **Goudie, A., Dynan, L., Brady, P.W. and Rettiganti, M., (2014):** Attributable cost and length of stay for central line–associated bloodstream infections. Pediatrics; 133(6), pp.e1525-e1532.
8. **Graus, J.M., Herbozo, C., Hernandez, R., Pantoja, A.F. and Zegarra, J., (2022):** Managing antibiotics wisely in a neonatal intensive care unit in a low resource setting. Journal of Perinatology; pp.1-6.
9. **Hammoud, M.S., Al-Taiar, A., Al-Abdi, S.Y., Bozaid, H., Khan, A., AlMuhairi, L.M., Rehman, M.U., (2017):** Late-onset neonatal sepsis in Arab states in the Gulf region: two-year prospective study. International Journal of Infectious Diseases;55, pp.125-130.
10. **Karagiannidou, S., Triantafyllou, C., Zaoutis, T.E., Papaevangelou, V., Maniadakis, N. and Kourlaba, G., (2020):** Length of stay, cost, and mortality of healthcare-acquired bloodstream infections in children and neonates: A systematic review and meta-analysis. Infection Control & Hospital Epidemiology; 41(3), pp.342-354.
11. **Mais, A., Hajar, F. and Rajab, M., (2015):** A quality improvement program to reduce central line associated blood stream infections in neonates. Br J Med Med Res; 7(8), pp.638-646.
12. **Parienti, J.J., Mongardon, N., Mégarbane, B., Mira, J.P., Kalfon, P., Gros, A., et**

al., (2015): Intravascular complications of central venous catheterization by insertion site. New England Journal of Medicine; 373(13), pp.1220-1229.

13. **Rabie, D., Mostafa, M.F., Abdel Halim, R.M. and Ezzat, O.A., (2022):** Central line-associated bloodstream infection (CLABSI) with three different vascular access in neonatal intensive care unit. Egyptian Pediatric Association Gazette; 70(1), pp.1-7.
14. **Rosenthal, V.D., (2009):** Central line-associated bloodstream infections in limited-resource countries: a review of the literature. Clinical Infectious Diseases; 49(12), pp.1899-1907.
15. **Różańska, A., Wójkowska-Mach, J., Adamski, P., Borszewska-Kornacka, M., Gulczyńska, E., Nowiczewski, M., et al., (2015):** Infections and risk-adjusted length of stay and hospital mortality in Polish Neonatology Intensive Care Units. International Journal of Infectious Diseases; 35, pp.87-92.
16. **Yaseen, M., Al-Hameed, F., Osman, K., Al-Janadi, M., Al-Shamrani, M., Al-Saedi, A. and Al-Thaqafi, A., (2016):** A project to reduce the rate of central line associated bloodstream infection in ICU patients to a target of zero. BMJ Open Quality; 5(1), pp.u212545-w4986.
17. **Zaidi, A.K., Huskins, W.C., Thaver, D., Bhutta, Z.A., Abbas, Z. and Goldmann, D.A., (2005):** Hospital-acquired neonatal infections in developing countries. The Lancet; 365(9465), pp.1175-1188.