IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

Open Access Original Article

# Peripherally Inserted Central Catheter Dwell Time as a Risk Factor of Central Line-Associated Bloodstream Infection in Neonates

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## ABSTRACT

***Background:*** According to the Centres for Disease Control and Prevention, central line-associated bloodstream infection (CLABSI) is a laboratory-confirmed bloodstream infection not related to an infection at another site that develops within 48 h of central line placement. Central line-associated bloodstream infection in the Neonatal Intensive Care Unit contributes to increased morbidity and hospital mortality. This study aimed to prove the relationship between peripherally inserted central catheter dwell time and the incidence of CLABSI among neonates at our tertiary center hospital in Bali, Indonesia.

***Methods:*** This study was conducted based on a prospective cohort study design. The subjects were neonates admitted in levels 2 and 3 of the neonatology wards of Sanglah Hospital, Bali, Indonesia, between November 2018 to December 2020. The cases were followed during the insertion of a central catheter. Statistical analysis was performed using the Chi-square test and logistic regression with a p-value of < 0.05.

***Results:*** Subjects were recruited consecutively and fulfilled the research criteria as many as 114 people. A total of 63 subjects were excluded, and none of the cases was lost for follow-up. The incidence rate of CLABSI was obtained at 19.2‰ among the 114 subjects. The patients with a catheter dwell time of > 14 days, compared to those with a catheter dwell time of ≤ 14 days, had a 2.9-fold risk of experiencing CLABSI (95% confidence interval: 1.191-7.497, P=0.02). No other risk factors were found for CLABSI development.

***Conclusion:*** The results of this study demonstrated that the risk of CLABSI in subjects with a catheter dwell time of > 14 days was 2.9. Therefore, the implementation of the CLABSI bundle is necessary to decrease CLABSI incidence in neonates.

***Keywords:*** CLABSI, Dwell time, Neonates, PICC

## Introduction

Healthcare-associated infections (HAIs) are associated with significant morbidity and mortality in intensive care units (1). According to the Centers for Disease Control and Prevention (CDC), central line-associated bloodstream infections (CLABSIs) are considered the deadliest HAIs (2). Central line-associated bloodstream infection is one of the serious healthcare-associated infections that cause excessive costs, morbidity, and mortality; however, CLABSI has been prevented in numerous developed and developing countries using multicenter approaches. There are several guidelines available for the prevention of CLABSI; nevertheless, the core contents of the evidence-based recommendations are shared. The National Healthcare Safety Network reports CLABSI incidence in developing countries at about 44.6/1000 central venous catheters per day (3). In India, it is said to be 7.9/1000 installations, and in Malaysia, there is an incidence rate of 6.4/1000 dwell time (1). Central line-associated bloodstream infections related to peripherally inserted central catheter (PICC) placement were reported at 1.1-19.3% per 1000 catheter installations (4). Data on CLABSI incidence is still not widely found in Indonesia and is lacking at our center, Sanglah General Hospital, Bali, Indonesia.

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*Please cite this paper as:*
Ekaputri DS, Sukmawati M, Sidiartha IGL Nilawati GAP, Utama IMGDL, Gustawan IW. Peripherally Inserted Central Catheter Dwell Time as a Risk Factor of Central Line-Associated Bloodstream Infection in Neonates. Iranian Journal of Neonatology. 2022 Apr: 13(2). DOI: 10.22038/IJN.2022.60748.2157

There is controversy over catheter dwell time that can increase the risk of CLABSI. Currently, the recommendation for central venous catheter dwell time is 35 days (2). In research by Hoang et al. (4), the median length of infection related to catheter installation was obtained at 13 days (length of insertion was 8-22 days). In another research by Cartwright (5), the median length of catheter-related infections was reported at 14 days. In previous studies, the type of widely found microbe was coagulase-negative staphylococci (4, 6). This study was conducted to investigate the relationship between PICC dwell time and CLABSI incidence among neonates at our tertiary center hospital in Bali, Indonesia.

## Methods

This prospective cohort study was conducted in the neonatology ward of the Sanglah General Hospital from November 2018 to December 2020. The dependent variable was CLABSI events. Follow-up was performed prospectively until patients were diagnosed with CLABSI. Subjects in this study were all 0-28-day-old neonates who met the criteria within the study period and were selected to be included.

The eligible subjects were the neonates who had PICC inserted within 48 h before the development of infection and had markers of infection at the beginning of PICC placement within normal limits. Moreover, parents/ guardians were required to agree that their child be included in the study voluntarily by signing informed consent. However, the subjects with major congenital abnormalities and positive blood culture before PICC placement were excluded from the study.

The samples were selected using the consecutive sampling method. The minimum sample size was estimated at 110 cases. The data from the study included gender, referral status, gestational age, birth weight, delivery method, surgery, ventilator usage, sites of placement, primary diagnosis, and outcome. The operational definitions of the variables were as follows: 1) CLABSI was a laboratory-confirmed bloodstream infection not related to an infection at another site that developed within 48 h of a central line placement; 2) markers of infection were categorized as abnormal if there were at least 2 out of 4 conditions below: leukocytes of < 5,000 or > 35,000/(neutropenia of < 1,500 or neutrophilia (>35% of WBCs), platelets of <150,000 ng/mL, procalcitonin 0.05 ng/mL, immature to total neutrophil ratio of > 0.2; 3) clinical manifestation was based on CDC criteria as follows: hypothermia, hyperthermia, apnea, or bradycardia; and 4) catheter dwell time was the number of days from line insertion until either line removal or day of CLABSI. This study was approved by the Research Ethics Committee of the School of Medicine, Universitas Udayana, Indonesia (2519/UN.14. 2.2.VII.14/LP/2018). Figure 1 shows the schematic diagram of this research.

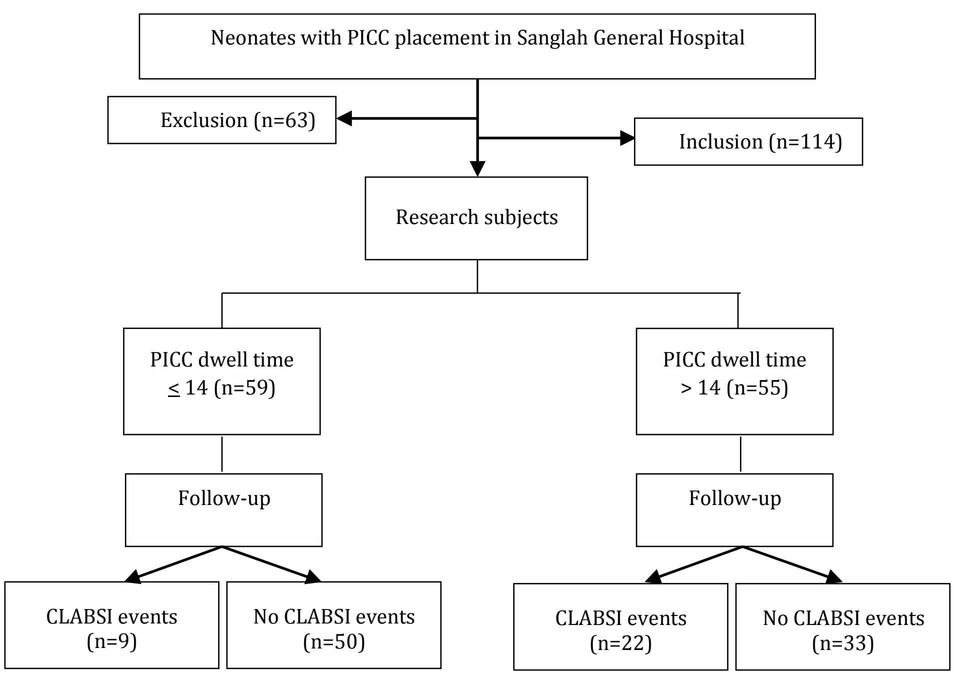

**Figure 1.** Schematic diagram of the research

## Results

The total population of the study consisted of 177 individuals. A total of 114 individuals met the research criteria after being recruited consecutively. None of the 63 excluded subjects (37 subjects due to positive blood culture and 26 subjects because of major congenital abnormalities) were lost to follow-up. The incidence rate of CLABSI was found at 19.2‰ in this study. The research subjects consisted of 65 boys and 49 girls. Of the 114 subjects, 31 (27.2%) cases were classified as having CLABSI. The characteristics of subjects based on catheter dwell time are presented in Table 1. The characteristics of the two groups did not appear to be significantly different.

Table 2 summarizes the etiology of CLABSI. Table 3 tabulates the clinical manifestation of subjects with CLABSI. Table 4 shows the relationship between catheter dwell time and CLABSI incidence. Subjects who experienced CLABSI ended up having a catheter dwell time of more than 14 days, and statistically significant differences were found between the two groups. Table 5 describes the multivariate analysis of the factors associated with CLABSI. There were no other important risk factors associated with CLABSI.

**Table 1.** Demographic characteristics of the subjects

| Characteristics | Dwell time of ≤14 days (n=59) | Dwell time of >14 days (n=55) | Total (n=114) |
|---|---|---|---|
| Gender, n (%) | | | |
| Male | 34 (52.3) | 31 (47.7) | 65 (57) |
| Female | 25 (51) | 24 (49) | 49 (43) |
| Referral status, n (%) | | | |
| Referral | 33 (50) | 33 (50) | 66 (57.8) |
| Non-referral | 26 (54.1) | 22 (45.9) | 48 (42.1) |
| Gestational age (weeks), n (%) | | | |
| Term (≥37) | 14 (73.6) | 5 (26.4) | 19 (16.7) |
| Moderate preterm (32-36) | 21 (50) | 21 (50) | 42 (36.8) |
| Very preterm (28-31) | 15 (50) | 15 (50) | 30 (26.4) |
| Extremely preterm (<28) | 9 (39.1) | 14 (60.9) | 23 (20.1) |
| Birth weight (g), n (%) | | | |
| Normal (2,500-4,000) | 6 (60) | 4 (40) | 10 (8.7) |
| LBW (1,500-2,499) | 22 (61.1) | 14 (38.9) | 36 (31.5) |
| VLBW (1,000-1,499) | 20 (52.6) | 18 (47.4) | 38 (33.4) |
| ELBW (<1,000) | 11 (36.6) | 19 (63.4) | 30 (26.4) |
| Delivery methods, n (%) | | | |
| Normal | 28 (56) | 22 (44) | 50 (43.8) |
| C-section | 30 (46.8) | 34 (53.2) | 64 (56.2) |
| Surgery, n (%) | | | |
| Yes | 11 (68.75) | 5 (31.25) | 16 (14) |
| No | 48 (48.9) | 50 (51.1) | 98 (86) |
| Ventilator use, n (%) | | | |
| Yes | 43 (51.8) | 40 (48.2) | 83 (72.8) |
| No | 16 (51.6) | 15 (48.4) | 31 (27.2) |
| Comorbid, n (%) | | | |
| Respiratory problem | 21 (53.8) | 18 (46.2) | 38 (33.4) |
| Necrotizing enterocolitis | 12 (63.1) | 9 (36.9) | 21 (18.4) |
| Intra-abdominal abnormality | 8 (44.4) | 10 (55.5) | 18 (15.7) |
| Congenital heart defect | 7 (50) | 7 (50) | 14 (12.2) |
| Neurology problem | 5 (50) | 5 (50) | 10 (8.8) |
| Meconium aspiration syndrome | 2 (50) | 2 (50) | 4 (3.5) |
| Others | 4 (50) | 4 (50) | 8 (7) |
| Site | | | |
| Upper extremities | 36 (53.7) | 31 (46.3) | 67 (58.7) |
| Lower extremities | 23 (48.9) | 24 (51.1) | 47 (41.3) |
| CLABSI | | | |
| Yes, n (%) | 9 (29) | 22 (71) | 31 (27.2) |
| No, n (%) | 50 (60.2) | 33 (39.8) | 83 (72.8) |
| Outcome | | | |
| Survive, n (%) | 49 (55) | 40 (45) | 89 (78) |
| Mortality, n (%) | 10 (40) | 15 (60) | 25 (22) |

LBW: Low birth weight; VLBW: Very low birth weight; ELBW: Extremely low birth weight; CLABSI: Central-line associated bloodstream infection

**Table 2.** CLABSI etiology

| Microorganisms | Total n=31 |
|---|---|
| Coagulase-Negative Staphylococci | 11 |
| *Klebsiella pneumonia* | 7 |
| *Acinetobacter baumannii* | 4 |
| *Enterococcus* spp. | 2 |
| *Pseudomonas aeruginosa* | 2 |
| *Acinetobacter lwoffii* | 1 |
| *Escherichia coli* | 1 |
| *Enterobacter cloacae* | 1 |
| Others | 2 |

CLABSI: Central-line associated bloodstream infection

**Table 3.** Clinical manifestations of CLABSI subjects

| Clinical manifestations | n=31 |
|---|---|
| Hyperthermia, n (%) | 4 (12.8) |
| Hypothermia, n (%) | 7 (22.4) |
| Apnea, n (%) | 2 (6.4) |
| Bradicardia (heart rate of <80 times/min), n (%) | 3 (10) |
| More than one manifestation, n (%) | 13 (42) |
| Others, n (%) | 2 (6.4) |

CLABSI: Central-line associated bloodstream infection

**Table 4.** Relationship between PICC dwell time and CLABSI events

| Dwell time | CLABSI | | RR (95% CI) | P-value |
|---|---|---|---|---|
| | Yes | No | | |
| Dwell time of >14 days, n (%) | 22 (40) | 33 (60) | 2.622 (1.324-5.191) | 0.003 |
| Dwell time of ≤14 days, n (%) | 9 (15.2) | 50 (84.8) | | |

PICC: Peripherally Inserted Central Catheter; CLABSI: Central-line associated bloodstream infection; RR: Relative risk; CI: Confidence Interval

**Table 5.** Multivariate analysis of other factors contributing to CLABSI

| Variable | b | RR (95% CI) | P-value |
|---|---|---|---|
| Male gender | 0.141 | 1.151 (0.473-2.804) | 0.756 |
| Prematurity | -1.472 | 0.229 (0.026-2.047) | 0.187 |
| Low birth weight | 2.144 | 8.536 (0.828-88.045) | 0.072 |
| Referral | -0.798 | 0.45 (0.186-1.089) | 0.077 |
| C-section methods | -0.143 | 0.866 (0.354-2.123) | 0.754 |
| Surgical action | 0.174 | 1.190 (0.301-4.696) | 0.804 |
| Upper extremities insertion | -0.156 | 0.855 (0.340-2.153) | 0.740 |
| Mechanical ventilation | -0.079 | 0.924 (0.351-2.435) | 0.873 |
| Dwell time of >14 days | 1.095 | 2.988 (1.191-7.497) | 0.020 |

CLABSI: Central-line associated bloodstream infection; RR: Relative risk; CI: Confidence Interval

## Discussion

The incidence of CLABSI is determined as the rate in per-mil units (‰). In this study, the CLABSI rate per 1,000 patient-day was estimated at 19.2‰. This figure was still very high compared to CLABSI obtained in studies conducted in other countries (7-9). In research performed at the central hospital in Saudi Arabia, the CLABSI rate was reported at 3.2‰, which then dropped to 2.7‰ after the application of the CLABSI bundle (9). The results of a study in the Netherlands indicated a higher result of CLABSI (9.0‰) in the absence of the bundle (7).

Care bundles are a collection of interventions that when implemented collectively will improve patient outcomes (2). There are several specific bundles that can be applied at healthcare facilities in resource-limited settings. There is a considerable amount of literature stating that the incidence of CLABSI can be reduced by the best practices, protocols, and checklists and by establishing a culture of patient safety. Moreover, it has been shown that the effective implementation of central line insertion and maintenance bundles can decrease the incidence of CLABSI until 'zero CLABSI' is achieved (7).

The reason for the high incidence of CLABSI in this study was probably related to the fact that the prevention of the CLABSI bundle was not implemented optimally. Data at Sanglah Hospital related to handwashing compliance were not routinely reported; therefore, it could not be evaluated as a contributing factor to the high incidence of CLABSI. The second point is that personal protective equipment before the catheter installation was routinely installed in the Neonatal Intensive Care Unit. Thirdly, antiseptics in the form of chlorhexidine were not routinely used at the beginning of the study because of their limited availability at hospitals. Fourthly, aseptic techniques were employed regularly under the applicable standard procedures. Finally, central venous catheters were monitored regularly using a checklist according to the standard method.

Other factors that also played a role in the incidence rate of high CLABSI in this study were the frequent increase in the number of patients that caused imbalances in the nurse-patient ratio, the behavior of health workers in handling patients, the procurement of tools, and the use of infusion catheters with closed systems that were not always consistently available. Factors outside the bundle that can contribute to CLABSI include environmental factors, such as room conditions (ceiling leaks) and air humidity in the neonatological treatment room, and other resource factors, such as hospital policy and tool procurement, which were not further analyzed in the study.

The microorganisms in this study were primarily coagulase-negative staphylococci (CoNS). This follows several other studies showing CoNS was the most common cause of CLABSI (10, 11). A seven-year multicenter study of CLABSI conducted by the U.S. Nationwide Surveillance and Control of Pathogens of Epidemiological Importance found that CoNS and Staphylococcus aureus caused 31% and 20% of CLABSI, respectively (12).

Coagulase-negative staphylococci are among the pathogens closely related to medical procedures in hospitals. They are gram-positive bacteria, a normal flora on the skin, previously considered a contaminant in the blood culture. Although they are not aggressive organisms, they have enzyme activity that can fight the body's defenses and cause numerous infections, especially in neonates less than a month and low birth weight newborns. In addition, microorganisms with negative coagulase have a higher chance of anti-microbial resistance and cause high mortality and morbidity (10, 13).

The next organism primarily found in the study was Klebsiella pneumoniae. This gram-negative bacterium has an essential role because the source of the decolonization channel increases due to the translocation of bacteria from the gastrointestinal tract, especially in neonates who undergo abdominal surgery or do not immediately receive enteral nutrients (14). In this study, fungi were not found as microorganisms causing CLABSI.

The symptoms and signs of CLABSI result from the complex processes of the interaction between pathogens and devotees. According to the work guide proposed by the CDC, CLABSI symptoms include hyperthermia, hypothermia, apnea, or bradycardia (2). These four symptoms are the typical symptoms for CLABSI caused by CoNS, S. aureus, and Candida species after removing other sources of the infection (12). The results of a study reported that most subjects (42%) showed more than one of those symptoms (12).

In the current study, most subjects had an infection on the 17th day of installation, as evidenced by positive blood culture. This supports the theory of CLABSI pathogenesis indicating that formed biofilms can be spread into blood vessels at least on the 11th day (15). Initially, the catheter is inserted into the blood vessels. Afterward, the surface of the catheter will be coated by plasma proteins and will form a fibrin sheath. When microorganisms enter through intraluminal and extraluminal routes, they are attached to the end of the catheter producing biofilms as a protector of the immune system (polymorphonuclear [PMN]) and antibiotics. If the host has good immunity, microorganisms circulating in blood vessels can be engulfed by PMN and leukocytes; nevertheless, if the body's immunity decreases, the infection can develop (15).

In this study, the earliest and latest days of central catheter insertion causing CLABSI were on days 3 and 28, respectively. None of the subjects had PICC placement of more than 28 days. The results of previous research have revealed that although the most optimal duration of using central venous catheters in neonates has not been found, the long-term use increases the chances of bacteria colonization in the central venous catheter, which eventually gives rise to positive blood culture (16). The findings of research by Sengupta et al. (17) and the CDC recommend replacing central venous catheters in less than 35 days to reduce the risk of CLABSI (16).

The results of this study demonstrated that the length of installation of >14 days had a strong relationship with CLABSI. Subjects with more than 14-day installation length experienced CLABSI by 40%, while those with a shorter duration than that suffered from CLABSI by 15.2%. In the present study, the relative risk of experiencing CLABSI was 2.9 times, with a 95% confidence interval between 1.191 and 7.497.

Based on the findings of a study by De Brito et al. (18), the risk of infection increased on the 16th day of installation. Research by Hsu et al. (19) obtained similar results; accordingly, CLABSI incidence increased after PICC dwell time of more than 20 days. Milstone et al. (15) identified a dwell time of more than 9 days as a significant risk factor for the onset of CLABSI with a relative risk of 3. The findings of research by Sengupta et al. (17) revealed that the risk of infection increased at 1-18 days of installation; however, the infection followed a decreasing trend on days 19-35 of installation, then increased by 33% every day after the day 35 of installation.

The use of a central venous catheter in neonatology at our center was evaluated daily until the longest use (30 days), unless there were complications or not necessary anymore, in that case, the catheter was removed as soon as possible. In this study, the risk of CLABSI increased if central venous catheters were employed for more than 14 days; regarding this, vigilance was needed in monitoring the conditions of neonates requiring catheter installation for more than 14 days.

In this research, CLABSI was routinely diagnosed in the neonate; so far, CLABSI is still generally diagnosed as neonatal sepsis. The study did not assess the possibility of infection with HAIs other than CLABSI, which can be external factors contributing to the subject's conditions, such as ventilator-associated pneumonia or urinary tract infections. In the current study, there was no follow-up examination related to microorganisms that cause CLABSI, in terms of examining microorganisms identified in the blood like those found in the patient's skin flora.

## Conclusion

Based on the results of this study, the CLABSI rate in our neonatology ward was reported at 19.2‰. It was revealed that the PICC dwell time of more than 14 days increased the risk of CLABSI by 2.9 times. The implementation of the CLABSI bundle program is essential to reduce the incidence rate of CLABSI. Further prospective cohort studies are needed on external predictor factors of mortality in CLABSI patients.

## Acknowledgments

The authors acknowledge the support received from all neonatology supervisors and neonatology ward staff for their help in this research.

## Conflicts of interest

The authors declare that there are no conflicts of interest.

## Funding

This study was not funded by any institution.

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