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Original Article

Analysis of Central Line-associated Bloodstream Infection among Infants in the Neonatal Intensive Care Unit: A Single Center Study

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Purpose: This study aimed to determine the incidence of central line-associated bloodstream infection (CLABSI) in the neonatal intensive care unit (NICU), evaluate the patients' clinical characteristics, and identify the etiologic agents for guidance in prevention and treatment.
Methods: A retrospective chart review study of infants classified as having CLABSI was conducted at the NICU of Seoul National University Bundang Hospital from January 2016 to December 2020.
Results: Of the 45 infants, 53 had CLABSIs within a follow-up period of 18,622 catheter days. The incidence of CLABSIs was 2.85 per 1,000 catheter days. The most common catheter type was a peripherally inserted central catheter (n=47, 81%). A total of 57 pathogens were isolated, of which 57.9% (n=33) were Gram-positive bacteria, 36.8% (n=21) were Gram-negative bacteria, and 5.3% (n=3) were *Candida* spp. The most common pathogens were *Staphylococcus aureus* (n=12, 21%) and coagulase-negative staphylococci (n=12, 21%), followed by *Klebsiella aerogenes* (n=8, 14%). The median duration of bacteremia was 2 days, and 19 episodes showed bacteremia for 3 days or more. The mortality rate of infants within 14 days of CLABSI was 13.3% (n=6).
Conclusions: This study analyzed the incidence of CLABSI and the distribution of pathogens in the NICU. Continuous monitoring of CLABSI based on active surveillance serves as guidance for empiric antibiotic use and also serves as a tool to assess the necessity for implementation of prevention strategies and their impact.

Keywords: Catheter-related infection; Central venous catheters; Intensive care units; Bacteremia; Neonatal sepsis

INTRODUCTION

The rate of premature birth has increased with maternal age and the development of treatment for infertility. Accordingly, the survival rate of premature babies has also increased with advances in treatment and critical care. Central lines (CLs) are widely used and attribute to the growth and survival of infants in the neonatal intensive care unit (NICU).[1] However,

Author Contributios

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the use of CLs may be accompanied by central line-associated bloodstream infection (CLABSI), an important cause of healthcare-associated infection (HAI), and is the a leading cause of morbidity and mortality in the NICU.[2] HAIs, such as CLABSI, are also associated with a significant burden on the healthcare system with substantial costs.[3,4] Prevention strategies for CLABSI include bundles for the insertion and maintenance of CLs. Efforts to control CLABSI should also be based on the assessment of local epidemiology. Surveillance is not only important for proper guidance of empirical antibiotics, but also serves as a tool to assess the necessity for implementation of prevention strategies and their impact.

Although studies on CLABSI in NICUs in other countries are available, only a limited number of studies have been conducted in Korea.[5-9] Thus, this study aimed to evaluate the incidence of CLABSI, clinical characteristics of patients with CLABSI, and microbiological data of CLABSI in patients admitted to the NICU at a tertiary medical center in Korea for 5 years.

MATERIALS AND METHODS

1. Study population and hospital setting

The study was conducted by retrospectively reviewing the medical records of infants in the NICU who experienced bloodstream infection (BSI) and were classified as having CLABSI in the hospital-wide surveillance system. These infants were admitted to the NICU of Seoul National University Bundang Hospital (SNUBH) between January 2016 and December 2020.

The NICU at SNUBH is a level III NICU[10] that cares yearly for approximately 500 infants with critical medical and surgical conditions who were born at either SNUBH or affiliated community sites.

Surveillance for CLABSI in the NICU has been performed at SNUBH since 2014. All cases of bacteremia among patients with catheters were reviewed by a designated nurse and pediatric infectious disease physician and collected by the infection control department. The cases were reported to the Korean National Healthcare-associated Infection Surveillance System (KONIS). KONIS is a HAI reporting system for hospitals operated by the Korean Society for Healthcare-Associated Infection Control and Prevention since 2006.[11] In 2019, the KONIS-NICU was established as part of the KONIS.

2. Definitions

CLABSI was assessed according to the surveillance definition published by the KONIS-NICU manual in 2020, which is based on the definition used by the US National Healthcare Safety Network system.

CLABSI is defined as a BSI that occurs when a CL is maintained for more than 2 days and established on the day or the day before the infection. A BSI must meet at least one of the following diagnostic criteria. (1) A recognized pathogen isolated from one or more blood cultures, with no other related site of infection, or (2) the presence of signs and symptoms including at least one of the following: fever above 38°C, hypothermia below 36°C, apnea, and bradycardia (heart rate <100 beats/min). A normal dermatogen is separated from two or more independently collected blood samples, and the pathogen separated from blood is unrelated to other sites of infection.

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A CL is an intravascular catheter placed in the patient's heart, near the heart, or in one of the large vessels, regardless of the insertion site. In this study, the term CL includes peripherally inserted central catheters (PICCs), umbilical venous catheters (UVCs), umbilical artery catheters (UACs), and non-tunneled catheters.

Patients may develop more than one CLABSI episode. A new episode in a subject is defined as the isolation of a microorganism after the repeat infection timeframe (RIT). RIT is a 14-day timeframe during which no new infections of the same type have been reported. For example, if the date of an event of bacteremia is within the 14-day RIT, the event is excluded, and the two episodes are counted as a single event. In addition, if additional pathogens are identified during RIT, the pathogens are added to the original event. Polymicrobial bacteremia is defined as the case in which two or more bacteria are separated from other blood culture samples obtained simultaneously or within 24 hours, and superinfection is defined as the case in which two or more bacteria are separated at intervals of more than 24 hours and less than 14 days. Prolonged bacteremia is defined as bacteremia ≥3 days from the first positive blood culture.

All CLs were included in patients with multiple CLs in place on the day of infection. Thus, if a CLABSI occurred in the presence of multiple catheters (which occurred on four occasions), the CLABSI was attributed to both catheters. We defined dwell time as the number of days from line insertion to the day of CLABSI. The insertion date was calculated as day one.

3. Data collection

Birth weight, gestational age, sex, date of birth, and date of NICU admission were extracted from hospital databases and medical records. Microbiological data, symptoms, and signs were retrieved from medical records. Catheter characteristics included the type of catheter, catheter insertion and removal dates, and insertion location.

This study was approved by the institutional review board of SNUBH (IRB no. B-2104-676-101).

4. Statistical analysis

Descriptive analyses were performed to characterize the patient population by reporting the median values and interquartile ranges (IQRs) or percentages. The incidence of infection was measured as infection episodes per 1,000 catheter days. Statistical analyses were performed using SPSS software (version 26.0; SPSS Inc., Chicago, IL, USA).

RESULTS

1. Demographics and clinical characteristics

Between January 2016 and December 2020, a total of 45 infants with 53 episodes of CLABSIs were identified among 18,622 central catheter days of surveillance. The mean rate of CLABSI was 2.85 per 1,000 catheter days, with a daily mean of 10.2 catheter days and a catheter utilization rate of 40.5%.

The demographics and clinical characteristics of patients with CLABSIs are summarized in **Table 1**. Of the patients with CLABSIs, the median gestational age at birth was 26 weeks (IQR, 25–30 weeks; range, 22–38 weeks), and the median birth weight was 860 g (IQR, 630–1,120 g; range, 420–3,770 g). The median age at the time of CL insertion was 3 days (IQR, 1–21

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Table 1. Demographics and clinical characteristics of patients with CLABSIs

Variables	Values
Birth weight (g)	860 (630–1,120)
Gestational age at birth (wk)	26 (25–30)
Age at line insertion (day)	3 (1–21)
Weight at line insertion (g)	960 (675–1,590)
Sex*	45 (100.0)
Male	26 (57.8)
Female	19 (42.2)
Catheter type†	58 (100.0)
PICC	47 (81.0)
UVC/UAC	7 (12.1)
Others	4 (6.9)
Catheter insertion site†	58 (100.0)
Upper extremity	15 (25.9)
Lower extremity	32 (55.2)
Umbilicus	7 (12.1)
Internal jugular vein	2 (3.4)
Subclavian vein	2 (3.4)
Catheter dwell time (day)	18 (9–30)
Major surgery	13
Exploratory laparotomy	8
PDA ligation	4
EVD	1
Suture and ligation of thoracic duct	1
Mortality‡	11 (24.4)
14-day mortality	6
30-day mortality	6

Data are presented as number (%) or median (interquartile ranges).
Abbreviations: CLABSI, central line-associated bloodstream infection; PICC, peripherally inserted central catheter; UVC, umbilical venous catheter; UAC, umbilical artery catheter; PDA, patent ductus arteriosus; EVD, external ventricular drain.
*After the repeat infection timeframe, a new event was counted in the same patient. Of a total of 45 patients, there were three independent infection episodes in one patient and two in six patients. So a total number of CLABSI episodes was 53. †Of a total of 53 CLABSI episodes, one case had three catheters (UAC, UVC, and PICC) and three cases had two catheters (UAC and UVC, UAC and UVC, and PICCs on upper and lower extremity) simultaneously, resulting in a total number of 58 catheters. ‡The percentage of mortality was calculated based on the total number of patients (n=45).

days; range, 1–306 days), and the median weight at the time of CL insertion was 960 g (IQR, 675–1,590 g; range, 420–9,805 g). A total of 26 (57.8%) infants were males, and 13 (28.9%) underwent major surgery, of which eight underwent exploratory laparotomy. 42 (93.3%) infants were administered total parenteral nutrition, including lipid emulsion.

When comparing the differences in cases with CLABSI according to gestational age, birth weight, age in days when the CL was placed, and duration of CL placement, there were more patients with a gestational age <32 weeks compared with those ≥32 weeks. Patients with birth weight <1,500 g were more frequent than those with birth weight ≥1,500 g. More than half of patients were catheterized within a month of age. Event occurrences were most frequent on days 7–29 from line insertion. All descriptions are presented as numbers and percentages in **Table 2**.

2. Central line (number, type, site/dwell time, time to insertion)

Of a total of 53 CLABSI episodes, one case had three catheters and three cases had two catheters simultaneously, resulting in a total number of 58 catheters. The most common type was PICC, which accounted for 47 (81%) of cases. The most common insertion site was the lower extremity (55.2%). The lower extremities included ankles, calves, and knee area. There were no cases of insertion at the femoral site.

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Table 2. Analysis of the proportion of subjects according to clinical characteristics

Demographic characteristics	Frequency	Percentage (%)
Gestational age, wk	45	100.0
<32	39	82.2
≥32	6	17.8
Birth weight, g	45	100.0
<1,500	38	84.4
≥1,500	7	15.6
Chronologic age, d	53	100.0
<7	6	11.3
7–29	23	43.4
30–59	12	22.65
≥60	12	22.65
Days since line insertion	53	100.0
<7	10	18.9
7–29	30	56.6
30–59	10	18.9
≥60	3	5.6

The median time from line insertion to infection, so-called catheter dwell time, was 18 days (IQR, 9–30 days; range, 3–87 days).

3. Microbiology of CLABSI

Table 3 summarizes the CLABSI pathogens. A total of 57 pathogens were identified in 53 episodes. Among them, 49 cases (92.4%) were classified as having monomicrobial

Table 3. Causative microorganisms responsible for CLABSIs

Microorganism	Values
Gram-positive bacteria	33 (57.9)
Coagulase-negative staphylococci species†	12 (21.1)
Staphylococcus aureus	12 (21.1)
Methicillin-resistant*,†	6 (10.5)
Methicillin-susceptible	6 (10.5)
Enterococcus spp.	6 (10.5)
Enterococcus faecalis†	5 (8.8)
Enterococcus faecium	1 (1.8)
Lactobacillus spp.	1 (1.8)
*Streptococcus agalactiae**	1 (1.8)
Gram-negative bacteria	21 (36.8)
Enterobacteriaceae	17 (29.8)
*Klebsiella aerogenes**	8 (14.0)
Klebsiella pneumoniae	7 (12.3)
Enterobacter cloacae	1 (1.8)
Escherichia coli	1 (1.8)
NFGNB	4 (7.0)
Burkholderia cepacia	2 (3.5)
Pseudomonas aeruginosa	1 (1.8)
Ralstonia mannitolilytica	1 (1.8)
Neisseria spp.	1 (1.8)
Fungi	3 (5.3)
Candida albicans†	2 (3.5)
Candida krusei	1 (1.8)
Total	57 (100)

Values are presented as number (%).
Abbreviations: CLABSI, central line-associated bloodstream infection; NFGNB, nonfermenting gram-negative bacilli.
,†57 pathogens were isolated from 53 episodes of CLABSI in 45 patients. Among them, two cases were polymicrobial bacteremia (*K. aerogenes* and *S. agalactiae*, and *K. aerogenes* and methicillin-resistant *S. aureus*), and two cases were superinfection† (*E. faecalis* and methicillin-resistant *S. aureus*, and Coagulase-negative staphylococcus and *Candida albicans*).

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bacteremia, two cases (3.8%) were polymicrobial bacteremia, and two cases (3.8%) were superinfection. Among all CLABSIs, 57.9% were Gram-positive bacteria, 36.8% were Gram-negative bacteria, and 5.3% were *Candida* spp. The most common pathogens were *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), *Klebsiella aerogenes*, and *Klebsiella pneumoniae*.

Antimicrobial susceptibility testing results were available for all cases. The highest overall prevalence of antimicrobial resistance was found in CoNS (11/12, 91.7% methicillin-resistant), *S. aureus* (6/12, 50% methicillin-resistant), and *K. aerogenes* (3/8, 37.5% cefotaxime-resistant). All the *Enterococcus faecalis* isolates (n=5) were sensitive to ampicillin, whereas *Enterococcus faecium* isolate (n=1) was resistant to ampicillin and sensitive to vancomycin. All *K. pneumoniae* (n=7) and *Escherichia coli* (n=1) isolates were non-extended-spectrum β-lactamase producers and all sensitive to cefotaxime.

4. Prolonged bacteremia and mortality

Among all subjects, the median duration of bacteremia was 2 days (IQR, 1–5 days; range, 1–12 days), and 19 episodes (35.9%) showed bacteremia for more than 3 days. Among the subjects with prolonged bacteremia (≥3 days), the median gestational age at birth was 27 weeks (IQR: 25–30 weeks), and the median birth weight was 790 g (IQR: 640–1,120 g). The median dwell time was 11 days (IQR: 5–28 days), and the median duration of bacteremia was 6 days (IQR, 5–8 days; range, 4–12 days). Among 19 cases of prolonged bacteremia, 11 (57.9%) were prescribed appropriate antibiotics on day of infection, 3 (15.8%) with empirical antibiotics were not susceptible and antibiotics were initiated 1 to 6 days after the date of infection in 8 cases. In the three cases which initial empiric antibiotic selection was not appropriate, persistent bacteremia lasted for 6 days, 9 days, and 10 days. CVC was removed <3 days in 5 patients (26%). However, 14 patients (74%) did not have their CVC removed within 3 days and the median time to removal was 7 days (IQR 4.25-8.25). Among 19 patients with prolonged bacteremia including 2 cases of superinfection, the total number of causative pathogens was 21. Of which, 42.9% (n=9) were Gram-negative bacteria, 47.6% (n=10) were Gram-positive bacteria, and 9.5% (n=2) were candida species.

The mortality of infants with CLABSIs was 11 (24.4%), of which six died within 14 days of infection. The causative pathogens of the 6 cases all differed, 5 were monomicrobial (*E. faecalis,* methicillin-resistant coagulase-negative staphylococcus, *K. aerogenes, K. pneumoniae,* and *Candida krusei*) and 1 case was a polymicrobial infection (*K. aerogenes* and *S. agalactiae*). Among the cases with mortality within 14 days, 4 patients showed prolonged bacteremia.

DISCUSSION

Surveillance of CLABSI is important for the treatment and management of NICU patients who are vulnerable to infection. Identifying the demographic characteristics of patients who experienced CLABSI may help select patients who need more intensive monitoring for CL management, and surveillance of pathogens and antibiograms are important to develop guidelines regarding appropriate antibiotic use.

In this study analyzing etiological organisms, CoNS species and *S. aureus* were found to be the most common, each accounting for 21% of all CLABSIs. This is likely due to their properties to colonize human skin and mucous membranes, which may have many opportunities to become pathogens in predisposed patients, such as neonates and patients with catheters.[12,13]

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Although the proportion of each bacterial species was different, the overall distribution was consistent with the results of previous studies.[6,8,14] A previous report by a single center in Korea also reported that Gram-positive bacteria, such as those mentioned above, were more dominant than Gram-negative bacteria.[15]

However, Gram-negative bacilli are also well-described causes of HAIs in the NICU population.[16,17] Infants in the NICU are at high risk of colonization with Gram-negative bacteria acquired through gastrointestinal flora and from environmental or human sources.[18,19] In this study, 21 cases (36.8%) of infections were caused by Gram-negative bacteria, most of which were *K. aerogenes* and *K. pneumoniae*. In those caused by Gram-negative bacteria, the morbidity and mortality rates have been reported to be higher than those caused by Gram-positive bacteria,[20] which is why we need to pay greater attention and make an appropriate treatment plan to eradicate Gram-negative bacteria.

Monitoring antibiotic resistance is essential to optimize empiric antibiotic use. Antibiotic resistance has emerged as an important issue in hospital settings because of the extensive use and misuse of antibiotics.[21]

In our hospital, piperacillin/tazobactam, piperacillin/tazobactam plus vancomycin, and vancomycin plus meropenem are used as initial empirical antibiotics in neonates with CLs, selected according to the patient's clinical symptoms and past medical history. Antibiotics are promptly changed according to the gram stain and final culture reports. In our study, the empirical antibiotics used were inappropriate in 13 cases, most of which were piperacillin/tazobactam, and the ultimate antibiotic used was either vancomycin or meropenem. Pathogens included methicillin-resistant CoNS (n=2), methicillin-resistant *S. aureus* (n=6), non-susceptible to piperacillin-tazobactam *K. aerogenes* (n=3), and *Candida* spp. (n=2). Among the 11 cases of bacteremia, three showed prolonged bacteremia for ≥3 days, in which two were methicillin-resistant CoNS and one was non-susceptible to piperacillin-tazobactam *K. aerogenes*.

Considering the distribution of major pathogens in our hospital, increased coverage for methicillin resistance may be necessary when CLABSI is suspected. However, an increase in broad-spectrum antibiotics may lead to an increase in antibiotic pressure; therefore, judicious use of broad-spectrum antibiotics is important and should be used in selective cases with hemodynamic instability and clinical deterioration.

There were three cases of CLABSI caused by *Candida* species. All patients were less than 1,000 g at birth, less than 26 weeks of postmenstrual age, and within 2 weeks of postnatal age. Among the three cases, fungemia occurred in one patient who was not on prophylactic fluconazole, whereas breakthrough infection occurred in two patients on fluconazole prophylaxis. In the latter two patients, one eventually died due to the persistence of fungemia for more than 10 days, despite treatment with amphotericin B.

According to a recent review article, studies have demonstrated the safety benefits of fluconazole prophylaxis without the development of fungal resistance. Therefore, prophylactic antifungal agents may be used to reduce mortality and improve outcomes in high-risk preterm infants.[22,23] In our center, prophylactic fluconazole is used in infants weighing less than 1000 grams at birth and born before 25 weeks of gestation until CVC removal. However, even in cases of prophylactic antifungal therapy, breakthrough infection may occur. Therefore, broad-spectrum antifungal therapy should be considered in high-risk cases with suspected fungal infections.

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HAIs can be affected by several factors, and antibiotic sensitivity profiles may also change; thus, it is important to monitor and analyze antimicrobial susceptibilities to isolates from infants periodically. Surveillance networks, such as the KONIS-NICU, also play an important role for institutions to comply with continuous monitoring.

Previous studies have recommended not to insert a CL at the femoral site of low birth weight infants because of the high incidence of CLABSI and the high risk of thrombosis.[24] Following this recommendation, none of the patients included in this study had a CL inserted at the femoral site.

The 2011 guidelines for the prevention of intravascular catheter-related infections recommend that the optimal dwelling time for the prevention of CLABSI depends on the catheter type. The recommended total duration of catheterization does not exceed 5 days for a UAC and 14 days for a UVC. However, routine replacement of the PICC is not recommended.[24] In our study, the time from the placement of the CL to the occurrence of CLABSI was 18 days (IQR 9–30), which is similar to previous studies.[14,25-27] However, because only patients already diagnosed with CLABSI were analyzed, the risk association of dwell time could not be determined. Independently, the necessity of maintaining catheters must be reviewed daily to immediately remove them once they are no longer essential.

Risk factors for CLABSI have been studied in infants in the NICU. Among the studies, gestational age or birth weight did not seem to have a significant effect on CLABSI.[6,14] However, other studies have reported birth body weight and gestational age as risk factors.[28,29] In this study, we were not able to compare these risk factors as a control group was not included in this study. Moreover, 80% of infants with CLABSI were born with a gestational age under 32 weeks and had a birth body weight <1,500 g. This is probably related to the higher and longer need for CLs in these subjects. Further studies on the risk factors for CLABSI in neonates are needed.

There were no significant differences in gestational age, birth body weight, and catheter dwell time between the group (n=19) with prolonged bacteremia for 72 hours or more and the other group (n=33) with bacteremia for less than 72 h. In 11 of the 19 cases, negative conversion of bacterial growth was confirmed after line removal. Line removal and change are important policies for source control in CLABSIs. However, removing catheters from patients with limited vascular access is also a difficult and critical issue. Catheters should be removed in patients with prolonged bacteremia despite appropriate antimicrobial therapy and due to specific microorganisms, including Gram-negative bacteria, *S. aureus*, enterococci, fungi, and mycobacteria. In cases initially treated with catheter salvage, lines should be removed in cases of clinical deterioration and persistent or recurrent CLABSI.[24,28]

This study has some limitations. First, because this was a retrospective cohort study at a single institution conducted for 5 years, the total number of patients included was small and thus could not represent the general NICU patient population in Korea. Second, as this study included no control group of CL without BSI, the statistical significance of contributing factors leading to the increased risk of CLABSI could not be identified.

In summary, neonates in critical care are highly susceptible to infection, and there are many opportunities for HAI, particularly CLABSI, to occur, requiring continuous efforts to evaluate and improve the quality of infection control and management.

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Only few published studies tracking NICU-CLABSIs in Korea have been reported to date. Regular and continuous surveillance at each center will provide better solutions for preventing and managing infections in the future.

More studies are needed to analyze the frequency, causative organism, and clinical characteristics of patients with CLABSI in the NICU, as well as discuss the factors affecting mortality. The results of such studies will contribute to reducing the incidence of NICU-CLABSI and the development of effective and safe infection control strategies for infants.

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요약

목적: 본 연구는 신생아중환자실에서 중심정맥관 관련 혈류감염 발생률을 확인하고, 이러한 환자들의 임상적 특성 및 원인균에 대해 분석하여 향후 신생아중환자실 내 혈류감염 예방 및 치료 지침의 기초 자료로 활용하고자 수행되었다.
방법: 2016년 1월부터 2020년 12월까지 분당서울대학교병원 신생아중환자실에 입원한 환자 중 중심정맥관 관련 혈류감염이 발생한 환자들을 대상으로 후향적 의무기록 분석을 하였다.
결과: 5년의 연구 기간동안 총 45명의 환자에게서 53례의 중심정맥관 관련 혈류감염이 확인되었고, 18,622 카테터-일 동안 발생률은 1,000 카테터-일 당 2.85건이었다. 가장 흔한 중심정맥관 종류는 말초 혈관 삽입형 중심정맥관이었다. 총 57균주가 분리되었고, 이 중 그람 양성균, 그람 음성균, 진균이 각각 57.9% (n=33), 36.8% (n=21), 5.3% (n=3)이었다. 가장 흔한 균은 *Staphylococcus aureus* (n=12, 21%) 와 *coagulase-negative staphylococci* (n=12, 21%)였고, 그 다음으로는 *Klebsiella aerogenes* (n=8, 14%)였다. 균혈증 평균 지속시간은 2일이었고, 19건에서는 3일 이상 균혈증이 지속되었다. 균혈증 발생으로부터 14일 이내에 사망한 사례는 총 6건(13.3%)이었다.
결론: 본 연구에서는 신생아중환자실 내 중심정맥관 관련 혈류감염의 발생률과 원인균 분포에 대해 분석하였다. 중심정맥관 관련 혈류감염에 대한 지속적인 모니터링은 경험적 항생제 사용 지침을 수립하기 위한 중요한 기반이 될 수 있으며, 감염예방 지침 실행의 필요성 및 이에 따른 영향을 평가하는 데에 도움이 될 것으로 생각된다.

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