



신생아 중환자실에서의 중심정맥관 관련 감염의 역학: 신속 체계적 고찰

에르데네투야 볼로르마^{1*} · 강초록^{2*} · 최영준^{3,4} · 허주선^{3,5} · 조한나³

고려대학교 의과대학 예방의학교실¹, 서울대학교 간호대학², 고려대학교 안암병원 소아청소년과³, 고려대학교 알레르기면역연구소⁴, 고려대학교 나노재생재건연구소⁵

Epidemiology of Catheter-related Bloodstream Infections in Neonatal Intensive Care Units: A Rapid Systematic Literature Review

Erdenetuya Bolormaa^{1*}, Choryok Kang^{2*}, Young June Choe^{3,4}, Joo Seon Heo^{3,5}, Hannah Cho³

Department of Preventive Medicine, Korea University College of Medicine¹, College of Nursing, Seoul National University², Department of Pediatrics, Korea University Anam Hospital³, Allergy and Immunology Center, Korea University⁴, Institute of Nano, Regeneration, Reconstruction, Korea University College of Medicine, Korea University⁵, Seoul, Korea

Background: Catheter-related bloodstream infections (CRBSIs) are serious complications in neonatal intensive care units (NICUs). We aimed to assess the incidence of CRBSIs in NICUs worldwide and describe the causative organisms.

Methods: We searched PubMed, EMBASE, Cochrane, and KoreaMed databases. We included studies on CRBSIs in NICU settings with data on bacteremia. We performed a random-effects meta-analysis on CRBSI incidence in NICUs, stratified the data according to WHO regions. We compiled data on underlying organisms.

Results: Of the 692 studies identified, 71 published between 2011 and 2022 were considered eligible. The pooled incidence of CRBSI per 1000 catheter days in NICUs was 8.66 (95% confidence interval [CI], 7.19; 10.12). Stratifying by WHO regions, the CRBSI incidence per 1000 catheter days was 10.38 (95% CI, 3.86; 16.90) in the Eastern Mediterranean Region (EMR), 11.77 (95% CI, 9.20; 14.35) in the European Union Region (EUR), 5.94 (95% CI, 3.87; 8.00) in the Western Pacific Region (WPR), and 6.71 (95% CI, 4.39; 9.03) in the Region from the Americas (AMR). Of the 2887 bacterial strains, 73.4% (n=2118) were gram-positive bacteria, 18.9% (n=547) were gram-negative bacteria, and 7.8% (n=225) were fungi. Coagulase-negative Staphylococci (n=1380, 65.2%) were the most common pathogen among the gram-positive types, followed by *Staphylococcus aureus* (n=318, 15%). Among the CRBSI gram-negative cultures, *Klebsiella* spp. (n=201, 36.7%) was the primary pathogen.

Conclusion: We found a substantial burden of CRBSIs in NICUs across the globe. Our findings highlight the need to improve the implementation of global and local strategies to reduce CRBSIs in NICUs.

Key Words: Neonate, Bacteremia, Catheters, Infection control, Systematic review

Received March 15, 2023

Revised April 28, 2023

Accepted May 8, 2023

Corresponding author:

Young June Choe

E-mail: choey@korea.ac.kr

ORCID:

<https://orcid.org/0000-0003-2733-0715>

*Equally contributed to the manuscript.

Introduction

Central venous catheters are commonly used to admin-

ister medications and parenteral nutrition to vulnerable neonates in neonatal intensive care units (NICUs) [1]. A common and serious complication of central venous cath-



eters is a catheter-related bloodstream infection (CRBSI), which is the most common cause of late-onset sepsis and has an estimated mortality rate of 70% in infants [2]. Neonates are highly vulnerable to CRBSIs in NICUs; however, incidence estimates are lacking in many countries.

A previous systematic review and meta-analysis investigated the incidence of neonatal sepsis [3]; however, no systematic review on the global incidence of CRBSIs limited to NICU settings has been reported to date. The study sought to review neonatal sepsis and mortality across low- and middle-income countries; however, this is not specific to CRBSIs in the NICU [3]. Furthermore, no regional comparative study has investigated the incidence of CRBSIs in NICUs.

We conducted a systematic literature review to assess

the incidence of CRBSIs in NICUs worldwide and describe the causative organisms. We aimed to assess the global incidence of CRBSI, particularly in NICUs, and compile data on causative pathogens.

Materials and Methods

1. Search strategy

We searched PubMed, EMBASE, Cochrane, and KoreaMed databases using the following keywords: “catheter-related infection”, “CVC infection”, “CVC-related infection”, “CVC associated infection”, “central line infection”, “central line related infection”, “central line-associated infection”, “bacteremia”, “bloodstream

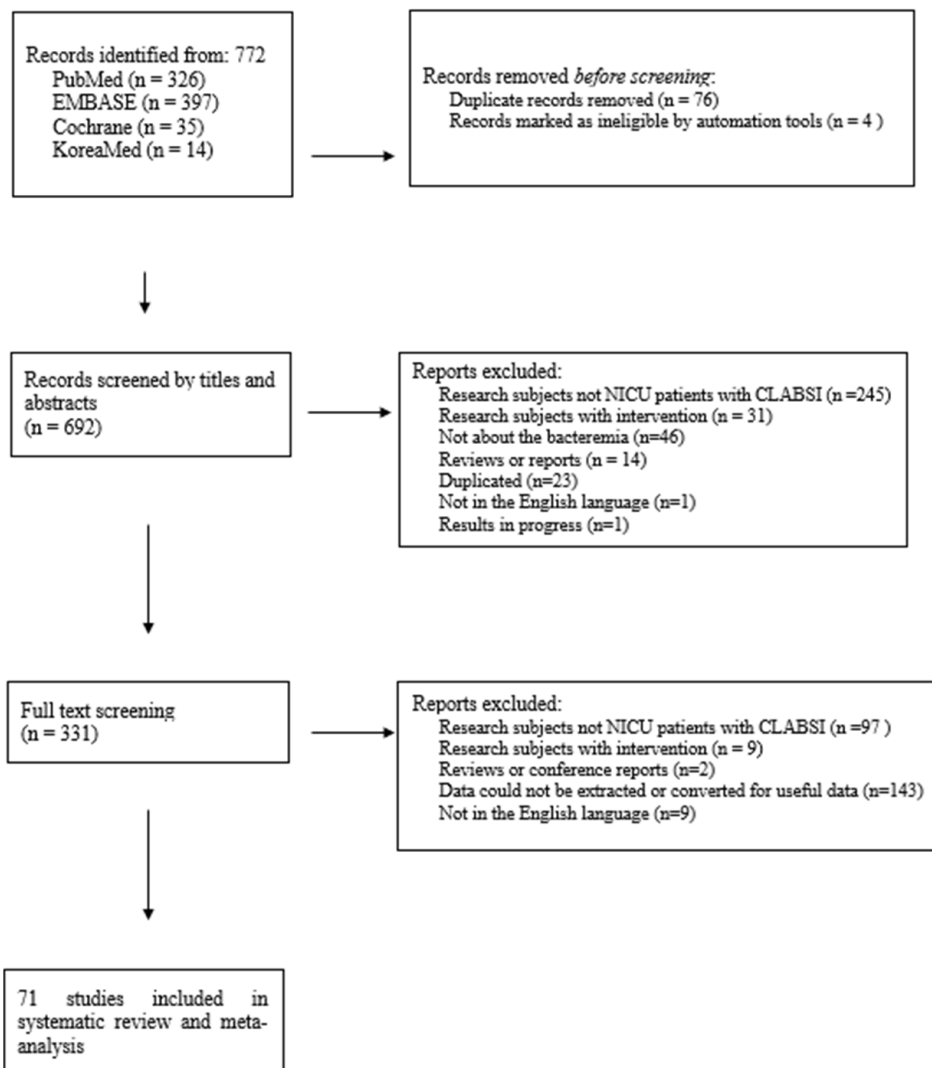


Fig. 1. Flowchart of the study selection.

Abbreviations: NICU, neonatal intensive care unit; CRBSI, catheter-related bloodstream infection.

Table 1. The characteristics of studies included in this systematic review

Ref No.	Study	No. of subjects	Study design	Country	Study year	Study population	CLABSI prevention	Incidence/1000 catheter-days
[4]	Al-Mousa et al.	671	Prospective cohort	Kuwait	2013-2015	Neonatal patients	None	15.3
[5]	Almeida et al.*	1194	Retrospective	Portugal	2007-2010	Newborn infants	Preventive bundle	14.1
[6]	Arnts et al.*	45	Prospective observational	Netherlands	2009-2010	Newborn infants	Preventive bundle	12.9
[7]	Bannatyne et al.*	406	Retrospective cohort	Australia	2011-2013	Newborn infants	Preventive bundle	8.8
[8]	Bierlaire et al.*	140	Prospective	Belgium	2019	Neonates	Preventive bundle	8.4
[9]	Blanchard et al.		Retrospective cohort	Canada	2007-2011	Neonatal patients	None	4
[10]	Bolat et al.	569	Prospective, cohort	Turkey	2009-2011	Neonatal patients	None	3.64
[11]	Boutaric et al.*	111	Prospective	France	2004-2006	Premature infants	Preventive protocol	16
[12]	Bunni et al.*	311	Retrospective	UK	2009	Neonates	Preventive bundle	22.4
[13]	Cabrera et al.	167	Prospective	Peru	2017-2018	Neonates	None	8
[14]	Callejas et al.	689	Retrospective	Canada	2010-2013	Neonates	None	5.6
[15]	Chandonnet et al.*		Prospective	USA	2011	Neonatal patients	Preventive bundle	2.6
[16]	Cheng et al.	123	Retrospective cohort	China	2011-2012	Neonates	None	4.99
[17]	Cheong et al.	39	Retrospective	Japan	2013	VLBW infants	None	3.57
[18]	Cleves et al.	1246	Retrospective, quasi-experimental	USA	2012-2014	Neonates	Chlorhexidine baths	8.64
[19]	Dumpa et al.*	68	Retrospective review	USA	2009-2010	Neonatal patients	Preventive bundle	4.4
[20]	Erdei et al.*		Prospective	USA	2009	Newborn infants	Preventive bundle	4.1
[21]	Ereno et al.	107	Retrospective	Singapore		Neonatal patients	None	5.9
[22]	Flidel-Rimon et al.*	141	Prospective	Israel	2011-2012	Infants	Preventive bundle	15.2
[23]	Fontela et al.		Retrospective dynamic cohort	Australia	2003-2009	Neonatal patients	None	4.4
[24]	Freeman et al.*	285	Retrospective	USA	2005-2012	Neonatal patients	Prevention protocol	1.69
[25]	Freitas et al.	1560	Prospective cohort	Brazil	2014-2016	Neonates	None	18.6
[26]	Gadallah et al.	434	Prospective cohort	Egypt	2012	Neonates	None	158.3
[27]	Gerver et al.		Retrospective	UK	2016-2017	Neonates	None	1.5
[28]	Greenhalgh et al.	176	Retrospective cohort	Australia	2012	Neonates	None	11.5
[29]	Hei et al.	131	Prospective	China	2008-2011	Neonatal patients	None	13.7
[30]	Helder et al.*	537	Prospective, observational	Netherlands	2014-2016	Infants	Antiseptic protocol	3.1
[31]	Hoevevar et al.		Retrospective	USA	2006-2008	Neonates	None	3.9
[32]	Holzmann-Pazgal et al.*		Retrospective	USA	2006-2008	Neonates	Line team	11.6
[33]	Hussain et al.	301	Prospective	Pakistan	2016	Neonatal patients	Preventive bundle	17.1
[34]	Hussain et al.	2046	Retrospective	Pakistan	2011-2015	Neonatal patients	None	8.9
[35]	Jansen et al.	180	Retrospective cohort	Netherlands	2015-2019	Preterm neonates	None	14
[36]	Jansen et al.	891	Retrospective cohort	Netherlands	2012-2020	Preterm neonates	None	13.4
[37]	Jeong et al.*	326	Retrospective	Korea	2011-2013	Neonatal patients	Preventive bundle	6.6
[38]	Kim et al.		Retrospective review	Korea	2016-2020	Infants	None	2.85
[39]	Kinoshita et al.	2383	Prospective observational	Japan	2014-2017	VLBW infants	None	2.1
[40]	Kleinlugtenbeld et al.*	75	Prospective	Netherlands	2007	Premature newborn	Preventive bundle	20.1

Table 1. Continued

Ref No.	Study	No. of subjects	Study design	Country	Study year	Study population	CLABSI prevention	Incidence/1000 catheter-days
[41]	Kourkouni et al.		Prospective	Greece		Neonatal patients	None	6.58
[42]	Kulali et al.*	70	Prospective cohort	Turkey	2016-2017	Neonatal patients	Preventive bundle	12.4
[43]	Leblebicioglu et al.	3430	Prospective	Turkey	2003-2012	Neonatal patients	None	21
[44]	Leistner et al.	5586	Prospective cohort	Germany	2008-2009	VLBW infants	None	8.3
[45]	Leveille et al.	1577	Retrospective cohort	Canada	2011-2016	Neonates	None	8.4
[46]	Milstone et al.	3967	Retrospective cohort	USA	2005-2010	Neonates	None	1.66
[47]	Mohamed Cassim et al.*	350	Retrospective cohort	UK	2010-2011	Newborn infants	Preventive bundle	4.3
[48]	Nercelles et al.	4704	Prospective	Chile	2005-2011	Newborn infants	None	0.9
[49]	Nielsen et al.	382	Retrospective	Denmark	2019-2020	Neonatal patients	None	13.41
[50]	Oh et al.	429	Retrospective	Korea	2017	Infants	Preventive bundle	1.89
[51]	Patrick et al.*		Prospective cohort	USA	2007-2012	Neonatal patients	None	2.1
[52]	Pavcnik-Armol et al.		Prospective cohort	Slovenia	2011-2012	Neonatal patients	None	5.5
[53]	Pharande et al.*	13731	Prospective	Australia	2002-2016	Newborn infants	Preventive bundle	12.04
[54]	Piazza et al.		Retrospective	USA	2011	Neonatal patients	None	1.333
[55]	Ponnusamy et al.	189	Prospective observational	UK	2009-2010	Infants	None	16.9
[56]	Rallis et al.*	94	Prospective	Greece	2012	Neonates	Preventive bundle	12
[57]	Resende et al.*	551	Prospective	Brazil	2010-2011	Infants	Preventive bundle	23
[58]	Rosenthal et al.*	2009	Prospective surveillance	El Salvador, Mexico, Philippines, Tunisia	2003	Neonatal patients	Preventive bundle	21.4
[59]	Salm et al.*	3028	Prospective cohort	Germany	2007-2009	VLBW infants	Preventive bundle	13.47
[60]	Sanderson et al.	4248	Prospective	Australia	2007-2009	Infants	None	10.6
[61]	Shalabi et al.	540	Retrospective matched cohort	Canada	2010-2013	Infants	None	8.5
[62]	Shepherd et al.*			USA	2003-2006	Infants	Preventive bundle	6
[63]	Sinha et al.*	152	Retrospective	UK	2007	Preterm neonates	Preventive bundle	26.5
[64]	Soares et al.	251	Retrospective cohort	Portugal	2014-2016	Neonatal patients	None	12.4
[65]	Steiner et al.*	526	Prospective	Germany	2010-2012	VLBW infants	Preventive bundle	8.96
[66]	Taylor et al.	83	Retrospective, quasi-experimental	Australia	2013-2017	Infants	None	13.8
[67]	Ting et al.*		Retrospective observational	Canada	2007-2008	Neonates	Preventive bundle	7.9
[68]	Wen et al.	301	Prospective	China	2010-2014	Premature infants	None	1.9
[69]	Wilder et al.*			USA	2011	Neonatal patients	Preventive bundle	3.9
[70]	Worth et al.		Prospective	Australia	2008-2016	Neonatal patients	None	2.2
[71]	Yalaz et al.	1200	Prospective	Turkey	2008-2010	Newborn infants	None	4.1
[72]	Yumani et al.	369	Retrospective	Netherlands	2007	Neonatal patients	None	18.1
[73]	Zachariah et al.		Cross-sectional	USA	2011	Neonatal patients	None	1.52
[74]	Zhou et al.	29	Prospective	China	2008-2010	Newborns	Preventive bundle	16.7

*Estimated only pre-intervention period CLABSI rate.

Abbreviation: VLBW, very low birth weight.

infection”, “neonatal intensive care”, “NICU”, “infant”, “neonate”, “newborn”, “newly born infant”, “neonatal infant”, “premature infant”, “preterm infant”, “low birth weight infant”, “LBW infant”, and “CRBSI”. We combined these terms with “AND” or “OR” when searching the databases. The search was performed on December 9, 2022.

2. Selection criteria

Studies were reviewed by their titles and abstracts in the first screening and by full-text articles in the second screening. The inclusion criteria were as follows: (1) the research participants included patients with CRBSIs, (2) all patients must have been admitted to the NICU, (3) the research participants had received no prior interventions, (4) the research was about microorganisms, and (5) the study was published in English. The exclusion criteria were as follows: (1) the study was duplicated, (2) the data could not be extracted or converted for useful data, (3) the studies were case reports, roundtable meeting reports, conference reports, or reviews, (4) the study was pub-

lished in languages other than English, and (5) the results were incomplete.

3. Data extraction

The information about the first author, published year, research time, country, data collection method, total patients in NICUs, total patients with CRBSIs, total catheter days, and total distribution of species and types of microorganisms was extracted by the review investigator with Microsoft Office Excel 2010.

4. Statistical analysis

The proportion of extracted data, the proportion of pathogens, and the pooled incidence and its 95% confidence intervals were analyzed using a meta package of R 4.2.2. A random effects model was chosen based on the heterogeneity and significance tests ($P < .05$, $I^2 > 50\%$). A subgroup analysis of regions divided by the World Health Organization (WHO) was conducted.

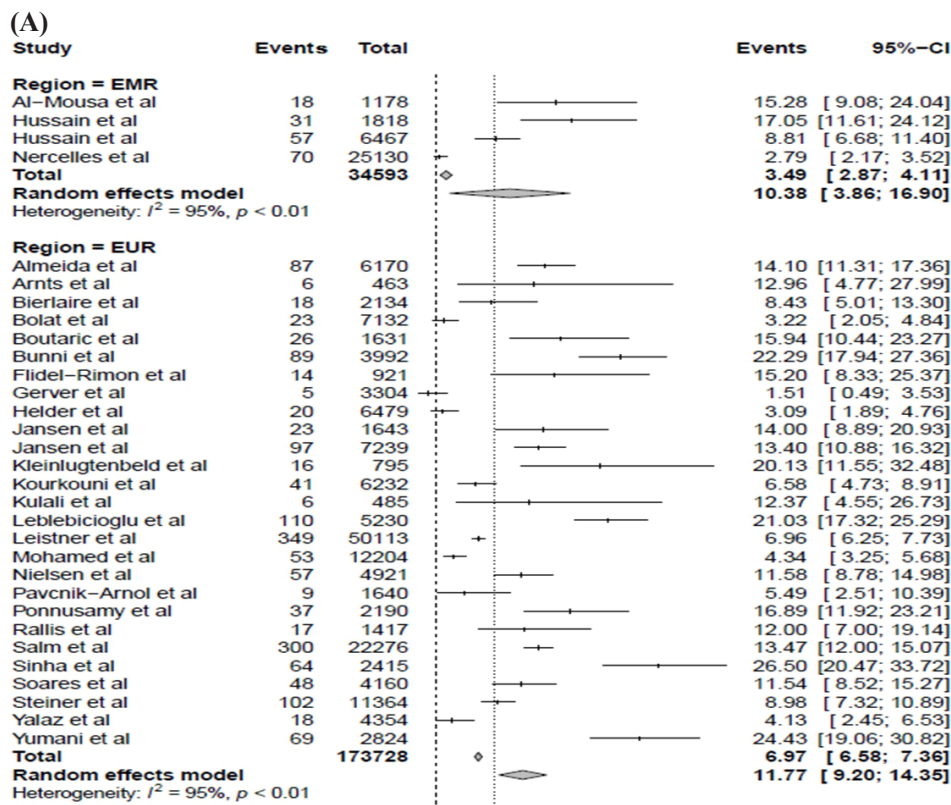


Fig. 2. Forest plot for catheter-related bloodstream infections per 1000 catheter days in the different World Health Organization regions, 2002-2020. (A) Eastern Mediterranean, Europe, (B) Western Pacific and Americas. Abbreviations: EMR, Eastern Mediterranean Region; EUR, European Union Region; WPR, Western Pacific Region; AMR, Region from America.

(B)

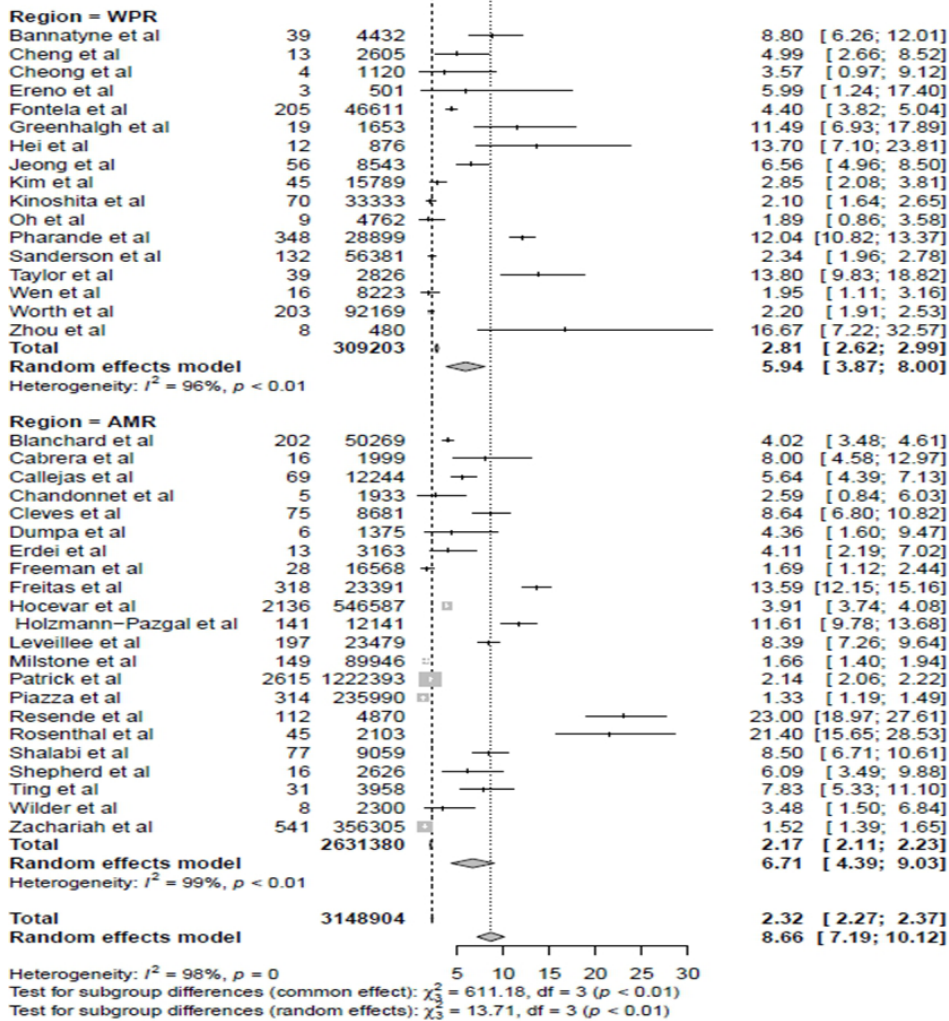


Fig. 2. Continued.

Results

1. Study selection

A total of 692 studies were first screened by their titles and abstracts, and 331 were selected for the next full-text screening. Among those, 97 studies did not involve patients with CRBSIs in NICUs, 9 recruited intervention participants, 2 studies were reviews, 9 were written in French and Chinese languages, and 143 did not have useful data for our meta-analysis of CRBSI incidence. Finally, 71 studies [4-74] were eligible for our analysis. We depicted the flowchart of the selection of surveys in Fig. 1.

Table 1 describes the selected studies on CRBSIs in NICUs.

2. Study characteristics

The 71 eligible studies were published from 2011-2022, mainly concentrated in 2012-2016. The surveys were conducted between 2002 and 2020. Dividing the studies by WHO regions, 22 (30.9%) were from the Region from the Americas (AMR) [9,13-15,18-20,24,25,31,32,45,46, 48,51,54,57,61,62,67,69,73], 5 (7.0%) from the Eastern Mediterranean Region (EMR) [4,26,33,34,58], 27 (38.0%) from the European Union Region (EUR) [5,6,8, 10-12,22,27,30,35,36,40-44,47,49,52,55,56,59,63-65,71,72], and 17 (23.9%) from the Western Pacific Region (WPR) [7,16,17,21,23,28,29,37-39,50,53,60,66,68, 70,74].

Most studies were from the United States ($n=13$,

18.3%) [15,18-20,24,31,32,46,51,54,62,69,73], Australia (n=7, 9.9%) [7,23,28,53,60,66,70], and the Netherlands (n=6, 8.5%) [6,30,35,36,40,72]. Regarding the methodology, 50.7% (n=36) were retrospective and 45.1% (n=32) were prospective studies. We included 63 082 patients in NICUs, except for 17 studies that did not provide information on the total number of patients with catheters.

3. The incidence of CRBSI

We estimated the pooled incidence of CRBSI per 1000 catheter days in NICUs by dividing the regions into subgroups. The CRBSI incidence per 1000 catheter days was 10.38 in the EMR (95% CI, 3.86; 16.90), 11.77 (95% CI, 9.20; 14.35) in the EUR, 5.94 (95% CI, 3.87; 8.00) in the WPR, and 6.71 (95% CI, 4.39; 9.03) in the AMR, and the total weighted CRBSI incidence per 1000 catheter days was 8.66 (95% CI, 7.19; 10.12) (Fig. 2).

Fig. 3 shows the trend of CRBSI per 1000 catheter days by an identified period of surveillance. The incidence of CRBSI per 1000 catheter days was 0.0-26.5, 1.9-23, and 1.5-17.1 in 2006-2010, 2011-2015, and 2016-2020, re-

spectively.

4. Distribution of pathogenic microorganisms

A total of 2887 bacterial strains were isolated from CRBSI samples. Among these, 73.4% (n=2118) were gram-positive bacteria, 18.9% (n=547) were gram-negative bacteria, and 7.8% (n=225) were fungi. Coagulase-negative Staphylococci (n=1380, 65.2%) was the most common pathogen among the gram-positive type, followed by *Staphylococcus aureus* (n=318, 15%), *Enterococcus* spp. (n=166, 7.8%), *Staphylococcus epidermidis* (n=88, 4.2%), and *Enterococcus faecalis* (n=64, 3%). Among the CRBSI gram-negative cultures, *Klebsiella* spp. (n=201, 36.7%) was the primary pathogen, followed by *Escherichia coli* (n=96, 17.6%) and *Enterobacter* spp. (n=64, 11.9%). *Candida species* (n=170, 75.6%) was primarily isolated among the fungi, and *Candida albicans* (n=33, 14.7%) and *Candida parapsilosis* (n=10, 4.4%) were most frequent among the CRBSI fungi isolates (Table 2).

Gram-positive species were the most common patho-

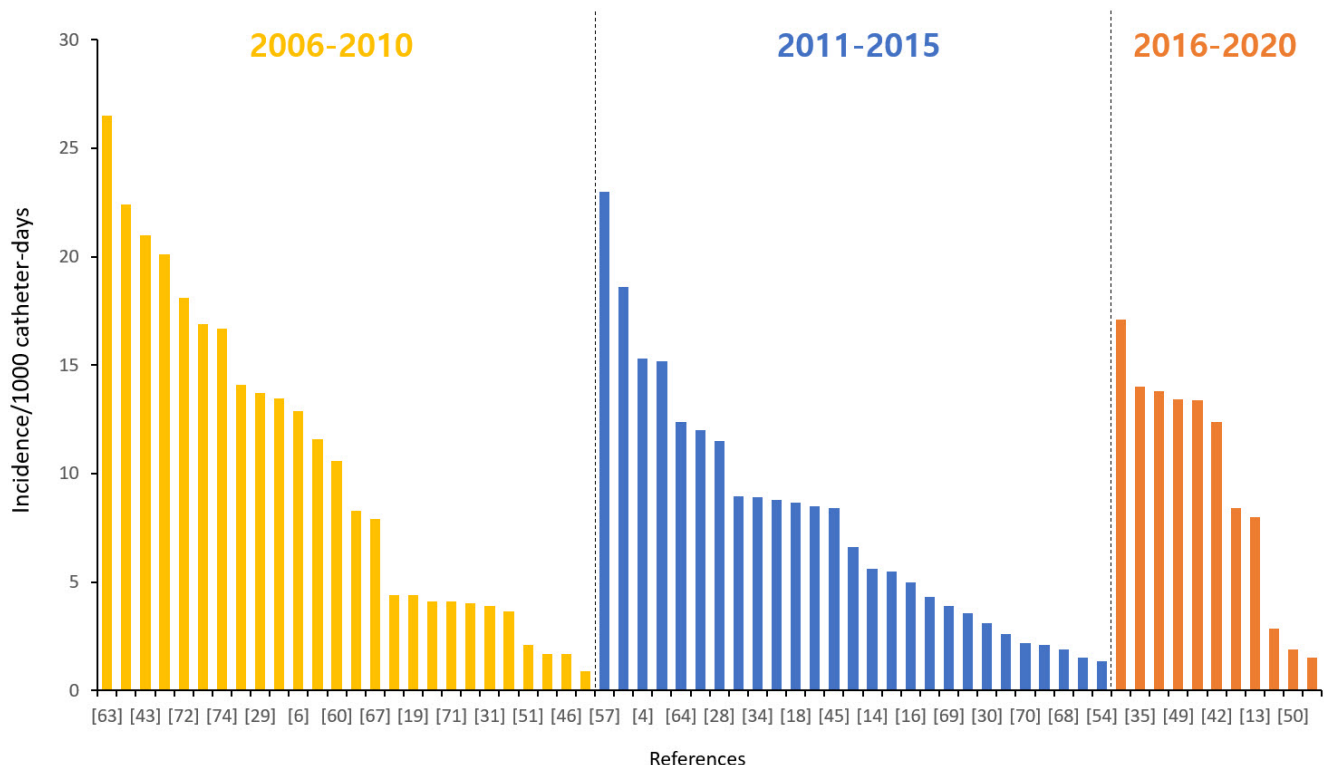


Fig. 3. Trend of catheter-related bloodstream infections per 1000 catheter days in neonatal intensive units by surveillance periods.

Table 2. The proportion of pathogen related to catheter-related bloodstream infection in neonatal intensive care unit (2006-2020)

Total pathogens (n=2887)	Frequency (%)
Gram-positive (n=2118)	
Coagulase-negative Staphylococci	1380 (65.2)
<i>Staphylococcus epidermidis</i>	88 (4.2)
<i>Staphylococcus capitis</i>	14 (0.7)
<i>Staphylococcus aureus</i>	333 (15.7)
Methicillin-resistant <i>Staphylococcus aureus</i>	14 (0.7)
Methicillin-sensitive <i>Staphylococcus aureus</i>	10 (0.5)
<i>Enterococcus</i> spp.	166 (7.8)
<i>Enterococcus faecalis</i>	64 (3)
<i>Streptococcus</i> spp.	19 (0.9)
<i>Bacillus</i> spp.	11 (0.5)
Other gram-positive	19 (0.9)
Gram-negative (n=547)	
<i>Klebsiella</i> spp.	201 (36.7)
<i>Klebsiella pneumoniae</i>	37 (6.8)
<i>Escherichia coli</i>	96 (17.6)
<i>Enterobacter</i> spp.	65 (11.9)
<i>Enterobacter cloacae</i>	6 (1.1)
<i>Pseudomonas aeruginosa</i>	32 (5.9)
<i>Acinetobacter baumannii</i>	24 (4.4)
<i>Serratia marcescens</i>	19 (3.5)
<i>Citrobacter freundii</i>	5 (0.9)
<i>Burkholderia cepacia</i>	3 (0.5)
<i>Pseudomonas fluorescens</i>	2 (0.4)
<i>Stenotrophomonas maltophilia</i>	2 (0.4)
<i>Citrobacter koseri</i>	2 (0.4)
Other gram-negative	53 (9.7)
Fungi (n=225)	
<i>Candida</i> spp.	170 (75.6)
<i>Candida albicans</i>	33 (14.7)
<i>Candida parapsilosis</i>	10 (4.4)
<i>Candida guillermundii</i>	5 (2.2)
<i>Candida lusitanae</i>	3 (1.3)
<i>Candida tropicalis</i>	2 (0.9)
<i>Candida glabrata</i>	2 (0.9)

gen type among CRBSI incidences in all three regions in our study, with proportions of 70% in the AMR, 76% in the WPR, and 84% in the EUR. Fig 4 describes the proportions of pathogen types among the subgroups of WHO regions. Among the EMR region surveys, no survey isolated pathogenic species. Approximately 20%, 21%, and 14% of the strains were gram-negative in the AMR, WPR, and EUR, respectively. Fungi was isolated in only 2% in EUR, 10% in AMR, and 3% in WPR.

Discussion

We analyzed a total of 71 studies and showed a substantial burden of CRBSIs in NICUs globally; however, our review was limited by a vast difference in terms of incidence rate, necessitating a standardized investigative method to report CRBSIs in NICUs. According to the National Healthcare Safety Network in the United States, only CLABSI in children ≤ 1 year is defined, which may not be suitable for neonates due to differences in the symptoms of infection [75]. This should motivate global researchers to define local NICU CRBSI definitions according to the standardized recommendations and sustainably implement such preventive measures. In this context, a modified case definition for CRBSI in NICU settings should be adapted from the previously defined “catheter-related bloodstream infection” or “central line-associated bloodstream infection” [76].

This systematic literature review is the first to investigate the global incidence of CRBSIs in NICUs. We estimated the CRBSI incidence with stratification according to WHO regions and identified regional differences in CRBSI incidence. In this study, incidence estimates were higher in the EMR and EUR than in the WPR and AMR. This finding indicates that the need to reduce CRBSIs in NICUs is greater in the EMR and EUR. Data from the African and Southeast Asian regions were not included in this study, which might lead to knowledge gaps on the global incidence of CRBSIs in NICUs. The incidence of neonatal sepsis is reported to be very high in the African region; however, the majority of hospital-wide and ICU-based studies have been conducted in high-income regions such as the European and American WHO regions [77]. Therefore, further studies are required to investigate the data from the African and Southeast Asian regions.

Furthermore, we found a downward trend in the incidence of CRBSIs in NICUs across countries. This may be explained by the adoption of CRBSI prevention bundles at multiple sites; however, this could not be determined from the current dataset. We propose a longitudinal analysis in defined clinical settings to investigate the role of prevention bundles in the incidence of CRBSIs in NICUs

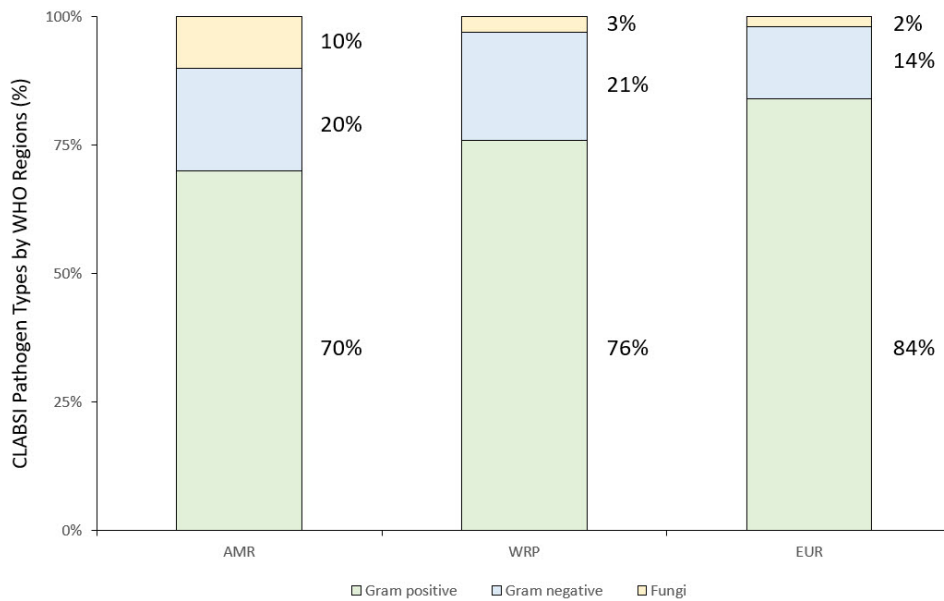


Fig. 4. The proportions of pathogens identified from catheter-related bloodstream infections in different World Health Organization regions, 2006-2016.

Abbreviations: AMR, Region from America; WPR, Western Pacific Region; EUR, European Union Region.

at different times.

In our study, the most common causative pathogens of CRBSIs in NICUs were coagulase-negative *Staphylococci*, *Staphylococcus aureus*, and *Klebsiella* spp. Our findings are consistent with a relevant study that estimated the global incidence of neonatal sepsis. This systematic review reported that the most commonly identified pathogens of neonatal sepsis were *Staphylococcus aureus* and *Klebsiella* spp. [3]. However, this review did not focus on NICU-based studies, and our study is the first to report the causative pathogens of CRBSI in NICUs worldwide.

Reducing neonatal mortality is an important component of the third Sustainable Development Goal. It is essential to understand the wide variability in neonatal health outcomes, particularly in NICUs across the globe. A recent systematic review showed that West and Central Africa and South Asia had the highest neonatal mortality rates in 2017, despite improvements from the 1990s [78]. A vast difference in neonatal mortality due to infectious causes between high- and low-income countries and regions is an important issue since the regionalization of neonatal healthcare is emphasized [79]. In this context, our study showed that neonatal CRBSI incidence was variable across countries, particularly in different settings. Higher incidences were observed in the Eastern Mediterranean and European regions compared to those of the Western Pacific and American regions. This difference may be

explained by the access to facilities for newborns, as previously described [80].

Our study was limited by the variability among individual studies, resulting in heterogeneity of the synthesized data, which required careful interpretation. Despite our broad search strategy with a focus on CRBSIs in NICUs, data from the African and Southeast Asian regions were not included in our study. This may be explained by a lack of epidemiological data, deficiencies in healthcare organizations and resources, and institutional obstacles to delivering critical care in the resource-limited settings of low-income countries. A recent systematic review showed that West and Central Africa and South Asia had the highest neonatal mortality rates in 2017, despite improvements from the 1990s [81]. Reducing neonatal mortality is an important component of the third Sustainable Development Goal. It is essential to understand the wide variability in neonatal health outcomes, particularly in NICUs across the globe.

We found a variable incidence of CRBSIs in NICUs globally, with a downward trend over the past 15 years; however, the substantial disease burden remains among newborns. Our findings highlight the need to improve the implementation of global and local strategies to reduce CRBSIs in NICUs. Future research is required to address the knowledge gaps identified by our study.

Acknowledgements

This study was supported by the Korean Society for Healthcare-Associated Infection Control and Prevention in 2021.

Disclosure of Conflict of Interest

The authors have no potential conflict of interest to disclose.

References

- Kochanowicz JF, Nowicka A, Al-Saad SR, Karbowski LM, Gadzinowski J, Szepecht D. Catheter-related bloodstream infections in infants hospitalized in neonatal intensive care units: a single center study. *Sci Rep* 2022;12: 13679.
- Singh L, Das S, Bhat VB, Plakkal N. Early neurodevelopmental outcome of very low birthweight neonates with culture-positive blood stream infection: a prospective cohort study. *Cureus* 2018;10:e3492.
- Fleischmann C, Reichert F, Cassini A, Horner R, Harder T, Markwart R, et al. Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis. *Arch Dis Child* 2021;106:745-52.
- Al-Mousa HH, Omar AA, Rosenthal VD, Salama MF, Aly NY, El-Dossoky Noweir M, et al. Device-associated infection rates, bacterial resistance, length of stay, and mortality in Kuwait: International Nosocomial Infection Consortium findings. *Am J Infect Control* 2016;44:444-9.
- Almeida CC, Pissarra da Silva SMS, Flor de Lima Caldas de Oliveira FSD, Guimarães Pereira Areias MHF. Nosocomial sepsis: evaluation of the efficacy of preventive measures in a level-III neonatal intensive care unit. *J Matern Fetal Neonatal Med* 2017;30:2036-41.
- Arnts IJ, Schrijvers NM, van der Flier M, Groenewoud JM, Antonius T, Liem KD. Central line bloodstream infections can be reduced in newborn infants using the modified Seldinger technique and care bundles of preventative measures. *Acta Paediatr* 2015;104:e152-7.
- Bannatyne M, Smith J, Panda M, Abdel-Latif ME, Chaudhari T. Retrospective cohort analysis of central line associated blood stream infection following introduction of a central line bundle in a neonatal intensive care unit. *Int J Pediatr* 2018;2018:4658181.
- Bierlaire S, Danhaive O, Carkeek K, Piersigilli F. 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. *Eur J Pediatr* 2021;180:449-60.
- Blanchard AC, Fortin E, Rocher I, Moore DL, Frenette C, Tremblay C, et al. Central line-associated bloodstream infection in neonatal intensive care units. *Infect Control Hosp Epidemiol* 2013;34:1167-73.
- Bolat F, Uslu S, Bolat G, Comert S, Can E, Bulbul A, et al. Healthcare-associated infections in a Neonatal Intensive Care Unit in Turkey. *Indian Pediatr* 2012;49:951-7.
- Boutaric E, Gilardi M, Cécile W, Fléchelles O. [Impact of clinical practice guidelines on the incidence of bloodstream infections related to peripherally inserted central venous catheter in preterm infants]. *Arch Pediatr* 2013; 20:130-6. French.
- Bunni L, Brunskill K, Parmar R, Townley P, Yoxall B. Reducing catheter associated blood stream infections in neonatal intensive care. *Arch Dis Child Fetal Neonatal Ed* 2014;99(Suppl 1):A71.
- Cabrera DM, Cuba FK, Hernández R, Prevost-Ruiz Y. Incidence and risk factors of central line catheter-related bloodstream infections. *Rev Peru Med Exp Salud Publica* 2021;38:95-100.
- Callejas A, Osiovič H, Ting JY. Use of peripherally inserted central catheters (PICC) via scalp veins in neonates. *J Matern Fetal Neonatal Med* 2016;29:3434-8.
- Chandonnet CJ, Kahlon PS, Rachh P, Degrazia M, Dewitt EC, Flaherty KA, et al. Health care failure mode and effect analysis to reduce NICU line-associated bloodstream infections. *Pediatrics* 2013;131:e1961-9.
- Cheng HY, Lu CY, Huang LM, Lee PI, Chen JM, Chang LY. Increased frequency of peripheral venipunctures raises the risk of central-line associated bloodstream infection in neonates with peripherally inserted central venous catheters. *J Microbiol Immunol Infect* 2016;49:230-6.
- Cheong SM, Totsu S, Nakanishi H, Uchiyama A, Kusuda S. Outcomes of peripherally inserted double lumen central catheter in very low birth weight infants. *J Neonatal Perinatal Med* 2016;9:99-105.
- Cleves D, Pino J, Patiño JA, Rosso F, Vélez JD, Pérez P. Effect of chlorhexidine baths on central-line-associated bloodstream infections in a neonatal intensive care unit in a developing country. *J Hosp Infect* 2018;100:e196-9.
- Dumpa V, Adler B, Allen D, Bowman D, Gram A, Ford P, et al. Reduction in central line-associated bloodstream infection rates after implementations of infection control measures at a level 3 neonatal intensive care unit. *Am J Med Qual* 2019;34:488-93.
- Erdei C, McAvoy LL, Gupta M, Pereira S, McGowan EC. Is zero central line-associated bloodstream infection rate sustainable? A 5-year perspective. *Pediatrics* 2015;135: e1485-93.
- Ereno IL, Yeo CL. Umbilical venous catheter (UVC) use in the neonates: the Singapore general hospital experi-

- ence. *J Paediatr Child Health* 2016;52(S2):32-3.
22. Flidel-Rimon O, Guri A, Levi D, Ciobotaro P, Oved M, Shinwell ES. Reduction of hospital-acquired infections in the neonatal intensive care unit: a long-term commitment. *Am J Infect Control* 2019;47:1002-5.
23. Fontela PS, Platt RW, Rocher I, Frenette C, Moore D, Fortin E, et al. Epidemiology of central line-associated bloodstream infections in Quebec intensive care units: a 6-year review. *Am J Infect Control* 2012;40:221-6.
24. Freeman JJ, Gadepalli SK, Siddiqui SM, Jarboe MD, Hirschl RB. Improving central line infection rates in the neonatal intensive care unit: effect of hospital location, site of insertion, and implementation of catheter-associated bloodstream infection protocols. *J Pediatr Surg* 2015; 50:860-3.
25. Freitas FTM, Araujo AFOL, Melo MIS, Romero GAS. Late-onset sepsis and mortality among neonates in a Brazilian Intensive Care Unit: a cohort study and survival analysis. *Epidemiol Infect* 2019;147:e208.
26. Gadallah MA, Aboul Fotouh AM, Habil IS, Imam SS, Wassef G. Surveillance of health care-associated infections in a tertiary hospital neonatal intensive care unit in Egypt: 1-year follow-up. *Am J Infect Control* 2014;42: 1207-11.
27. Gerver SM, Mihalkova M, Bion JF, Wilson APR, Chudasama D, Johnson AP, et al. Surveillance of bloodstream infections in intensive care units in England, May 2016-April 2017: epidemiology and ecology. *J Hosp Infect* 2020;106:1-9.
28. Greenhalgh M, Gordon A. Risk of CLABSI in neonates by PICC line dwell time. *J Paediatr Child Health* 2014; 50(Suppl 1):86.
29. Hei MY, Zhang XC, Gao XY, Zhao LL, Wu ZX, Tian L, et al. Catheter-related infection and pathogens of umbilical venous catheterization in a neonatal intensive care unit in China. *Am J Perinatol* 2012;29:107-14.
30. Helder OK, van Rosmalen J, van Dalen A, Schaffhuizen L, Vos MC, Flint RB, et al. Effect of the use of an antiseptic barrier cap on the rates of central line-associated bloodstream infections in neonatal and pediatric intensive care. *Am J Infect Control* 2020;48:1171-8.
31. Hocevar SN, Edwards JR, Horan TC, Morrell GC, Iwamoto M, Lessa FC. Device-associated infections among neonatal intensive care unit patients: incidence and associated pathogens reported to the National Healthcare Safety Network, 2006-2008. *Infect Control Hosp Epidemiol* 2012;33:1200-6.
32. Holzmann-Pazgal G, Kubanda A, Davis K, Khan AM, Brumley K, Denson SE. Utilizing a line maintenance team to reduce central-line-associated bloodstream infections in a neonatal intensive care unit. *J Perinatol* 2012; 32:281-6.
33. Hussain AS, Ariff S. 5 Year surveillance of clabsi in a tertiary care private sector nicu in Pakistan. *Antimicrob Resist Infect Control* 2017;6(Suppl 3):P211.
34. Hussain ASS, Ali SR, Ariff S, Arbab S, Demas S, Zeb J, et al. A protocol for quality improvement programme to reduce central line-associated bloodstream infections in NICU of low and middle income country. *BMJ Paediatr Open* 2017;1:e000008.
35. Jansen SJ, Lopriore E, Berkhout RJM, van der Hoeven A, Saccoccia B, de Boer JM, et al. The effect of single-room care versus open-bay care on the incidence of bacterial nosocomial infections in pre-term neonates: a retrospective cohort study. *Infect Dis Ther* 2021;10:373-86.
36. Jansen SJ, van der Hoeven A, van den Akker T, Veenhof M, von Asmuth EGJ, Veldkamp KE, et al. A longitudinal analysis of nosocomial bloodstream infections among preterm neonates. *Eur J Clin Microbiol Infect Dis* 2022; 41:1327-36.
37. Jeong IS, Park SM, Lee JM, Song JY, Lee SJ. Effect of central line bundle on central line-associated bloodstream infections in intensive care units. *Am J Infect Control* 2013;41:710-6.
38. Kim M, Choi S, Jung YH, Choi CW, Shin MJ, Kim ES, et al. Analysis of central line-associated bloodstream infection among infants in the neonatal intensive care unit: a single center study. *Pediatr Infect Vaccine* 2021;28:133-43.
39. Kinoshita D, Hada S, Fujita R, Matsunaga N, Sakaki H, Ohki Y. Maximal sterile barrier precautions independently contribute to decreased central line-associated bloodstream infection in very low birth weight infants: a prospective multicenter observational study. *Am J Infect Control* 2019;47:1365-9.
40. Kleinlugtenbeld OJ, van Straaten HLM, van den Bos MI, Hemels MAC, d'Haens EJ. Reduction in central line associated bloodstream infections by introducing a quality improvement pathway 'clean line'. *Arch Dis Child* 2012;97(Suppl 2):A497.
41. Kourkouni E, Kourlaba G, Chorianopoulou E, Tsopela GC, Kopsidas I, Spyridaki I, et al. Surveillance for central-line-associated bloodstream infections: accuracy of different sampling strategies. *Infect Control Hosp Epidemiol* 2018;39:1210-5.
42. Kulali F, Çalkavur Ş, Oruç Y, Demiray N, Devrim İ. Impact of central line bundle for prevention of umbilical catheter-related bloodstream infections in a neonatal intensive care unit: a pre-post intervention study. *Am J Infect Control* 2019;47:387-90.
43. Leblebicioglu H, Erben N, Rosenthal VD, Atasay B, Erbay A, Unal S, et al. International Nosocomial Infection Control Consortium (INICC) national report on device-associated infection rates in 19 cities of Turkey, data summary for 2003-2012. *Ann Clin Microbiol Antimicrob* 2014;13:51.

44. Leistner R, Thürnagel S, Schwab F, Piening B, Gastmeier P, Geffers C. The impact of staffing on central venous catheter-associated bloodstream infections in preterm neonates - results of nation-wide cohort study in Germany. *Antimicrob Resist Infect Control* 2013;2:11.
45. Leveillee A, Lapointe A, Lachance C, Descarries M, Autmizguine J, Dubois J, et al. Assessing effect of catheter type and position on central line-associated bloodstream infections in the NICU. *Paediatr Child Health* 2018; 23(Suppl 1):e59.
46. Milstone AM, Reich NG, Advani S, Yuan G, Bryant K, Coffin SE, et al. Catheter dwell time and CLABSI in neonates with PICCs: a multicenter cohort study. *Pediatrics* 2013;132:e1609-15.
47. Mohamed Cassim S, Skiffington C, Lucas C, Anand D. An improvement project to reduce central line associated blood stream infection (CLABSI) in newborn infants. *Arch Dis Child* 2015;100(Suppl 3):A238-9.
48. Nercelles P, Vernal S, Brenner P, Rivero P. [Risk of bacteremia associated with intravascular devices stratified by birth weight in born of a public hospital of high complexity: follow-up to seven years]. *Rev Chilena Infectol* 2015; 32:278-82. Spanish.
49. Nielsen CL, Zachariassen G, Holm KG. Central line-associated bloodstream infection in infants admitted to a level III neonatal intensive care unit. *Dan Med J* 2022;69: A05210463.
50. Oh Y, Oh KW, Lim G. Routine scrubbing reduced central line associated bloodstream infection in NICU. *Am J Infect Control* 2020;48:1179-83.
51. Patrick SW, Kawai AT, Kleinman K, Jin R, Vaz L, Gay C, et al. Health care-associated infections among critically ill children in the US, 2007-2012. *Pediatrics* 2014;134:705-12.
52. Pavcnik-Arnol M, Kalan G. Risk factors for central-line associated bloodstream infections in critically ill neonates. *Arch Dis Child* 2012;97(Suppl 2):A169.
53. Pharande P, Lindrea KB, Smyth J, Evans M, Lui K, Bolisetty S. Trends in late-onset sepsis in a neonatal intensive care unit following implementation of infection control bundle: a 15-year audit. *J Paediatr Child Health* 2018;54: 1314-20.
54. Piazza AJ, Brozanski B, Provost L, Grover TR, Chuo J, Smith JR, et al. SLUG bug: quality improvement with orchestrated testing leads to NICU CLABSI reduction. *Pediatrics* 2016;137:e20143642.
55. Ponnusamy V, Venkatesh V, Curley A, Musonda P, Brown N, Tremlett C, et al. Segmental percutaneous central venous line cultures for diagnosis of catheter-related sepsis. *Arch Dis Child Fetal Neonatal Ed* 2012;97:F273-8.
56. Rallis D, Karagianni P, Papakotoula I, Nikolaidis N, Tsakalidis C. Significant reduction of central line-associated bloodstream infection rates in a tertiary neonatal unit. *Am J Infect Control* 2016;44:485-7.
57. Resende DS, Peppe AL, dos Reis H, Abdallah VO, Ribas RM, Gontijo Filho PP. Late onset sepsis in newborn babies: epidemiology and effect of a bundle to prevent central line associated bloodstream infections in the neonatal intensive care unit. *Braz J Infect Dis* 2015;19:52-7.
58. Rosenthal VD, Dueñas L, Sobreyra-Oropeza M, Ammar K, Navoa-Ng JA, de Casares AC, et al. Findings of the International Nosocomial Infection Control Consortium (INICC), part III: effectiveness of a multidimensional infection control approach to reduce central line-associated bloodstream infections in the neonatal intensive care units of 4 developing countries. *Infect Control Hosp Epidemiol* 2013;34:229-37.
59. Salm F, Schwab F, Geffers C, Gastmeier P, Piening B. The implementation of an evidence-based bundle for bloodstream infections in neonatal intensive care units in Germany: a controlled intervention study to improve patient safety. *Infect Control Hosp Epidemiol* 2016;37:798-804.
60. Sanderson E, Bolisetty S, Bajuk B, Callander I, Abdel-Latif M, Lui K. Nosocomial sepsis in NICU - risks associated with duration and type of central venous catheters in NSW and the ACT. *J Paediatr Child Health* 2012; 48(Suppl 1):132.
61. Shalabi M, Adel M, Yoon E, Aziz K, Lee S, Shah PS. Risk of infection using peripherally inserted central and umbilical catheters in preterm neonates. *Pediatrics* 2015; 136:1073-9.
62. Shepherd EG, Kelly TJ, Vinsel JA, Cunningham DJ, Keels E, Beauseau W, et al. Significant reduction of central-line associated bloodstream infections in a network of diverse neonatal nurseries. *J Pediatr* 2015;167:41-6.e1-3.
63. Sinha AK, Murthy V, Nath P, Morris JK, Millar M. Prevention of late onset sepsis and central-line associated blood stream infection in preterm infants. *Pediatr Infect Dis J* 2016;35:401-6.
64. Soares BN, Pissarra S, Rouxinol-Dias AL, Costa S, Guimarães H. Complications of central lines in neonates admitted to a level III Neonatal Intensive Care Unit. *J Matern Fetal Neonatal Med* 2018;31:2770-6.
65. Steiner M, Langgartner M, Cardona F, Waldhör T, Schwindt J, Haiden N, et al. Significant reduction of catheter-associated blood stream infections in preterm neonates after implementation of a care bundle focusing on simulation training of central line insertion. *Pediatr Infect Dis J* 2015;34:1193-6.
66. Taylor JE, McDonald SJ, Earnest A, Buttery J, Fusinato B, Hovenden S, et al. A quality improvement initiative to reduce central line infection in neonates using checklists. *Eur J Pediatr* 2017;176:639-46.
67. Ting JY, Goh VS, Osioviich H. Reduction of central line-

- associated bloodstream infection rates in a neonatal intensive care unit after implementation of a multidisciplinary evidence-based quality improvement collaborative: a four-year surveillance. *Can J Infect Dis Med Microbiol* 2013;24:185-90.
68. Wen J, Yu Q, Chen H, Chen N, Huang S, Cai W. Peripherally inserted central venous catheter-associated complications exert negative effects on body weight gain in neonatal intensive care units. *Asia Pac J Clin Nutr* 2017;26:1-5.
 69. Wilder KA, Wall B, Haggard D, Epperson T. CLABSI reduction strategy: a systematic central line quality improvement initiative integrating line-rounding principles and a team approach. *Adv Neonatal Care* 2016;16:170-7.
 70. Worth LJ, Daley AJ, Spelman T, Bull AL, Brett JA, Richards MJ. Central and peripheral line-associated bloodstream infections in Australian neonatal and paediatric intensive care units: findings from a comprehensive Victorian surveillance network, 2008-2016. *J Hosp Infect* 2018;99:55-61.
 71. Yalaz M, Altun-Köroğlu O, Ulusoy B, Yildiz B, Akisu M, Vardar F, et al. Evaluation of device-associated infections in a neonatal intensive care unit. *Turk J Pediatr* 2012;54:128-35.
 72. Yumani DF, van den Dungen FA, van Weissenbruch MM. Incidence and risk factors for catheter-associated bloodstream infections in neonatal intensive care. *Acta Paediatr* 2013;102:e293-8.
 73. Zachariah P, Furuya EY, Edwards J, Dick A, Liu H, Herzig CT, et al. Compliance with prevention practices and their association with central line-associated bloodstream infections in neonatal intensive care units. *Am J Infect Control* 2014;42:847-51.
 74. Zhou Q, Lee SK, Hu XJ, Jiang SY, Chen C, Wang CQ, et al. Successful reduction in central line-associated bloodstream infections in a Chinese neonatal intensive care unit. *Am J Infect Control* 2015;43:275-9.
 75. Cho HJ, Cho HK. Central line-associated bloodstream infections in neonates. *Korean J Pediatr* 2019;62:79-84.
 76. Bell T, O'Grady NP. Prevention of central line-associated bloodstream infections. *Infect Dis Clin North Am* 2017;31:551-9.
 77. Diaz JV, Riviello ED, Papali A, Adhikari NKJ, Ferreira JC. Global critical care: moving forward in resource-limited settings. *Ann Glob Health* 2019;85:3.
 78. Hug L, Alexander M, You D, Alkema L; UN Inter-agency Group for Child Mortality Estimation. National, regional, and global levels and trends in neonatal mortality between 1990 and 2017, with scenario-based projections to 2030: a systematic analysis. *Lancet Glob Health* 2019;7:e710-20. Erratum in: *Lancet Glob Health* 2019;7:e1179.
 79. Saugstad OD. Reducing global neonatal mortality is possible. *Neonatology* 2011;99:250-7.
 80. Martinez AM, Khu DT, Boo NY, Neou L, Saysanasongkham B, Partridge JC. Barriers to neonatal care in developing countries: parents' and providers' perceptions. *J Paediatr Child Health* 2012;48:852-8.
 81. Markwart R, Saito H, Harder T, Tomczyk S, Cassini A, Fleischmann-Struzek C, et al. Epidemiology and burden of sepsis acquired in hospitals and intensive care units: a systematic review and meta-analysis. *Intensive Care Med* 2020;46:1536-51.