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ORIGINAL PAPER

CATHETER-ASSOCIATED BLOODSTREAM INFECTIONS IN A BULGARIAN NEONATAL INTENSIVE CARE UNIT

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Abstract

ABSTRACT

Introduction. Central and peripheral venous catheters are widely used for patients in the neonatal intensive care unit (NICU). However, intravascular devices are known to cause healthcare-associated infections (HAI).
The objective of the study was to characterize the profile of neonatal bloodstream infections in NICU, to improve their prevention.
Materials and methods. A prospective 18-month study was conducted. During the study period, 507 neonates were followed up prospectively. Data on demographic characteristics of the patients, underlying diseases, clinical symptoms, imaging studies, etiological agents isolated from clinical samples (endotracheal aspirates,

Résumé

Bactériémies associées à un cathéter dans une unité de soins intensifs néonatals bulgare

Introduction. Les cathéters veineux centraux et périphériques sont largement utilisés pour les patients de l'unité néonatale de soins intensifs (USIN), mais les dispositifs intravasculaires sont connus pour provoquer des infections nosocomiales.
L'objectif de l'étude était de caractériser le profil des bactériémies néonatales en USIN afin d'améliorer leur prévention.
Matériaux et méthodes. Une étude prospective de 18 mois a été menée. Au cours de la période d'étude, 507 nouveau-nés ont été suivis prospectivement. Des données sur les caractéristiques démographiques de

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blood cultures, ear secretions, wound samples), and antimicrobial susceptibility rates were recorded.
Results. During the study period, 13 patients with bloodstream infections were diagnosed. This type of infection ranks second in the distribution of HAI – 23.64% (1.81/ 1000 patient days). In the 13 patients studied, we calculated a mean birth weight of 2735.38±1120.644 grams and a mean gestational age of 36.3±4.96 weeks. The most common laboratory finding in patients with catheter-associated bloodstream infection (CABSI) was elevated C-reactive protein (CRP). The leading agent of bloodstream infections was *Coagulase-negative Staphylococcus*.
Conclusions. CABSI were the second most common HAI in the respective NICU. Future interventions should focus on developing training programs and applying bundles for prevention of CABSI.

Keywords: catheter-associated bloodstream infection, neonate, neonatal intensive care unit, sepsis, nosocomial infections.

List of abbreviations

CABSI – catheter-associated bloodstream infection
CRP – C-reactive protein
CVC – central venous catheter
HAI – healthcare-associated infection
NICU – neonatal intensive care unit
MIC – minimal inhibitory concentrations
PVC – peripheral venous catheter
UVC – umbilical venous catheter
VAP – ventilator-associated pneumonia

Résumé
Introduction. Les cathéters veineux centraux et périphériques sont largement utilisés chez les patients admis en unité de soins intensifs néonatals (USIN), pour fournir une voie d'administration sûre de fluides et de médicaments. Cependant, les dispositifs intravasculaires, en particulier les cathéters veineux centraux, sont connus pour causer des infections associées aux soins de santé (HAI). Ces infections dans la population néonatale sont associées à des résultats cliniques plus médiocres et à des coûts de santé significatifs. Les taux de bactériémies associées aux cathéters (CABSI) varient de 3,3 infections/1000 jours-cathéter pour les nourrissons avec un poids à la naissance <750 g à 1,4 infections/1000 jours-cathéter pour ceux pesant >2500 g à la naissance. Les facteurs de risque de CABSI comprennent un faible poids à la naissance, un âge gestationnel inférieur, une ventilation mécanique prolongée, une nutrition parentérale et un accès vasculaire. En ce qui concerne la microbiologie de CABSI, l'un des principaux pathogènes rapportés est les cocci Gram-positifs. Dans les pays en développement, les microorganismes Gram-négatifs peuvent être beaucoup plus prévalents en tant que pathogènes néonatals avec une incidence plus élevée de résistance aux antimicrobiens.
Le but de l'étude était de caractériser le profil des infections sanguines néonatales en USIN, afin d'améliorer leur prévention.
Matériaux et méthodes. Une étude prospective a été menée entre janvier 2017 et juin 2018 en USIN de l'hôpital universitaire "St George" Plovdiv, Bulgarie. Les données démographiques des patients, les maladies sous-jacentes, les symptômes cliniques, les études d'imagerie, les agents étiologiques isolés à partir d'échantillons cliniques (aspirations endotrachéales, hémocultures, sécrétions auriculaires, échantillons de plaies) et les taux de sensibilité aux antimicrobiens ont été enregistrées.
Résultats. Au cours de la période d'étude, 13 patients atteints d'infections du sang ont été diagnostiqués. Ce type d'infection occupe la deuxième place dans la distribution des infections nosocomiales – 23,64% (1,81/ 1000 jours-patients). Chez les 13 patientes étudiées, nous avons calculé un poids moyen à la naissance de 2735,38±1120,644 grammes et un âge gestationnel moyen de 36,3±4,96 semaines. Le résultat de laboratoire le plus courant chez les patients atteints de bactériémie associée à un cathéter était une protéine C-réactive élevée. Le principal agent causal des bactériémies était le staphylocoque à coagulase négative.
Conclusions. Conformément aux résultats de la présente étude, les bactériémies associées aux cathéters étaient les deuxièmes infections nosocomiales les plus courantes dans les USIN respectives. Les interventions futures devraient se concentrer sur le développement de programmes de formation et l'application de faisceaux pour la prévention des bactériémies associées aux cathéters.

Mots-clés: bactériémie associée à un cathéter, nouveau-né, unité de soins intensifs néonatals, septicémie, infections nosocomiales.

Introduction

Central and peripheral venous catheters are widely used in patients admitted in the neonatal intensive care unit (NICU), to provide a route for the safe administration of fluids and medications. However, intravascular devices, especially central venous catheters, are known to cause healthcare-associated infections (HAI)[1,2]. These infections in the neonatal population are associated with poorer clinical outcomes and significant healthcare costs[3]. The mean catheter-associated bloodstream infections (CABSI) rates range from 3.3 infections/1000 catheter-days for infants with birth weight <750 g to 1.4 infections/1000 catheter days for those weighing >2500 g at birth[4].

The risk factors for CABSI include low birth weight, lower gestational age, prolonged mechanical ventilation, parenteral nutrition, and vascular access[5-7]. Regarding the microbiology of CABSI, one of the leading pathogens reported are Gram-positive cocci[8-9]. In developing countries, Gram-negative microorganisms may be far more prevalent as neonatal pathogens with a higher incidence of antimicrobial resistance[10].

The objective of the study was to characterize the profile of neonatal bloodstream infections in NICU, to improve their prevention.

Materials and methods

Study period and setting

A prospective study was conducted between January 2017 – June 2018 in the NICU of the University Hospital "St George" Plovdiv, Bulgaria. The hospital is in the second largest Bulgarian city and the NICU is level 3 NICU in respect to the care provided for the patients.

Patients' characteristics

During the study period, 507 neonates were followed up prospectively (44.3% of whom were with a

birth weight under 2,500 grams). All neonates admitted to the ward for more than 48 hours and in whom a venous catheter was inserted for more than 72 hours were included in the study. During the study period, 13 patients with bloodstream infections were diagnosed. Data on demographic characteristics of these patients, underlying diseases, clinical symptoms, imaging studies, etiological agents isolated from clinical samples (endotracheal aspirates, blood cultures, ear secretions, wound samples), and antimicrobial susceptibility rates were recorded.

Definition and identification of bloodstream infection

As there are still no generally accepted criteria for diagnosing sepsis in children <1 year of age for the purposes of the study, after a landscape review of the literature, we developed a survey form for epidemiological surveillance. Bloodstream infection was defined as positive microbial growth on one or more blood cultures with accompanying clinical signs (temperature >38^{0}C, temperature instability or hypothermia (<36.5^{0}C), respiratory disorders (tachypnea, bradypnea, periods of apnea), cardiocirculatory disorders (bradycardia, tachycardia), metabolic and electrolyte disturbances (metabolic acidosis, hypoglycemia or hyperglycemia), other signs of sepsis (change in skin color, unstable condition, apathy) and laboratory findings suggestive of sepsis: C-reactive protein >10 mg/dL, abnormal white blood cells (leucocytes >30,000/mm^3 or leucocytes <5,000 mm^3), thrombocytopenia (<150,000/mm^3).

Microbiological methods

BACT/ALERT Media bottle were used for the recovery of microorganism from blood, incubated in BACT/ALERT 3D Microbial Detection System. Semi-automated (API 20NE, bioMerieux) and automated systems (Vitek-2 Compact, bioMerieux and MALDI-TOF MS, Vitek-MS, bioMerieux) were used for bacterial identification. Antimicrobial susceptibility testing was performed on Müller-Hinton agar by using the disk-diffusion method of Bauer-Kirby and by using E-test and broth microdilution test to determine the minimal inhibitory concentrations (MIC). Automated systems (Vitek-2 Compact, bioMerieux) were also utilized. Antimicrobial susceptibility reports were based on EUCAST criteria.

Statistical analysis

Quantitative variables are presented as mean ± standard deviation (mean ± SD) or median (25th percentile; 75th percentile) based on sample distribution. The Shapiro-Wilk test was used to inform about the distribution of the patients sampled. Categorical variables are presented as frequencies and percentages and compared using the Chi-square test. The p-values < 0.05 were considered statistically significant for all statistical tests. The systematization, processing and analysis were performed using SPSS v.25 for Windows.

The study received approval from the Ethics Committee of the Medical University of Plovdiv, Bulgaria (№ R –1595).

Results

During the study period, 507 neonates were prospectively studied, and their characteristics are summarized in Table 1. Fifty-four HAI were diagnosed in 48 (9.7%) of the newborns and 13 of them developed a bloodstream infection. This type of infection ranks

Table 1. Characteristics of the study population

Variable	*All patients (n=507)*	*Patients with CABSI (n=13)*
Mode of delivery, n (%) Vaginal,	185 (36.5)	7 (53.85)
Gender, n (%) Female	218 (43.0)	7 (53.85)
Birth weight (grams), (mean±SD)	2600.9±849.4	2735.4±1120.6
Gestational age (weeks), (mean±SD)	36.6±3.2	36.3±4.9
Resuscitation and intubation after delivery, n (%)	98 (19.33)	5 (38.46)
Time to infection (days), (mean±SD)	10.52±7.8	8.92±4.9
Total number of patient days (days)	7175	426
Length of hospital stay (days), median (25th;75th percentile)	12.1 (7.0;17.0)	25.0 (16.5;52.5)
Length of CVC/UVC use (days), median (25th;75th percentile)	3.2(2.0;3.0)	4.0 (2.0;13.0)
Length of PVC use (days), median (25th;75th percentile)	9.0 (6.0;15.0)	25.0 (14.5;49.5)
Length of antibiotic treatment (days), median (25th;75th percentile)	9.0 (6.0;14.0)	23.0 (14.5;49.0)

Table 2. Clinical and laboratory findings in patients with a bloodstream infection

Finding	*n (%)*
Respiratory disorders	8 (61.54)
Temperature instability	8 (61.54)
Hypoglycemic episodes	7 (55.56)
Leukocytosis	5 (38.46)
Elevated CRP	11 (84.61)
Thrombocytopenia	5 (38.46)

Table 3. Microorganisms, isolated from hemoculture from patients with bloodstream infection

Microorganism	*n (%)*
Gram-positive	
Coagulase-negative Staphylococcus spp.	11 (64.72)
Enterococcus faecium	2 (11.76)
Enterococcus faecalis	1 (5.88)
Gram-negative	
E. coli	1 (5.88)
*Enterobacter cloacae ESBL+**	1 (5.88)
Acinetobacter lwolffii	1 (5.88)
Overall isolated 1microorganisms	17 (100)
***ESBLs – extended-spectrum beta-lactamases**	

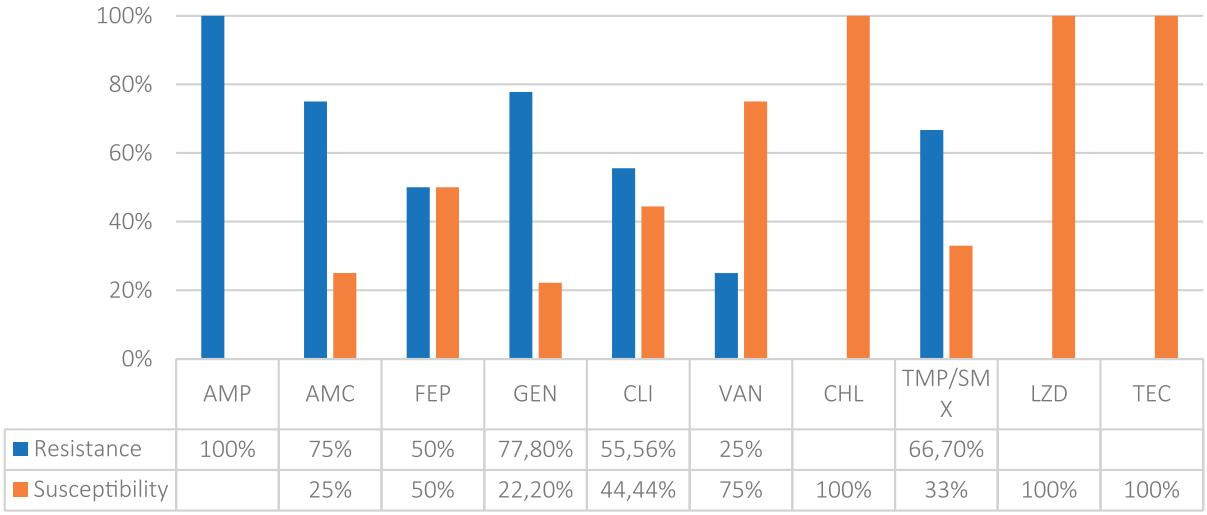


Figure 1. Antibiotic resistance of *Coagulase-negative Staphylococcus spp.*

* AMP – ampicillin; AMC – amoxicillin/clavulanic acid, FEP – cefepime; GEN- gentamicin;, CLI – clindamycin; VAN – vancomycin; CHL – chloramphenicol; LZD – linezolid; TEC – teicoplanin

second in the distribution of HAI – 23.64% (1.81/ 1000 patient days), after ventilator-associated pneumonia – 67.27% (35.06/ 1000 ventilator days). In 12 infants, the infection was associated with the presence of an invasive device (central venous catheter (CVC), umbilical venous catheter (UVC) or peripheral venous catheter (PVC)) and in one infant clinical sepsis was diagnosed. Additionally, in three infants more than one nosocomial infection occurred: two ventilator-associated pneumonias (VAP) and one conjunctivitis. During the study period, one of the 13 neonates died, which resulted in a mortality rate of 7.7%.

The mean birth weight in the 13 patients included in the study group was 2735.38±1120.644 grams which corresponds with the mean birth weight of all 507 neonates (2600.9±849.4 grams). The number of babies with birth weight <2500 grams was 5 out of 13 (38.46%).

The clinical and laboratory findings in patients with bloodstream infection are shown in Table 2. In the 13 neonates, 45 blood cultures were tested (Table 3). In total, 17 microorganisms were isolated and identified as being the cause of bloodstream infections. Gram-positive microorganisms outnumbered the Gram-negative microorganisms (82.35%), with *Coagulase (-) Staphylococcus spp.* having the highest relative share (Table 2). There was no leading causative agent among the Gram-negative microorganisms, and they had a much lower relative share (17.65%).

We observed a significant resistance of *Coagulase (-) Staphylococcus spp.* to Ampicillin and Gentamicin (Figure 1). Simultaneously, Chloramphenicol, Linezolid,

and Teicoplanin sensitivity was completely preserved. Vancomycin sensitivity was confirmed in 75% of all isolates.

Discussion

According to the literature, bloodstream infections are the most common nosocomial infections[10-12] and represent 3-28% of hospital admissions in NICUs[13,14], most of them being associated with the presence of an invasive device. The reported incidence of bloodstream infections in our study, 24.07% (1.81/1000 patient days), ranks this type of infection as second in the HAI structure of the NICU, and this trend is maintained during the prospective study and in a 5-year retrospective study from 2012 to 2016[15]. Following the most recent data available from 2014[16], bloodstream infections in neonatology wards rank fourth in Bulgaria, after infections of the sensory organs (ears, eyes, nose), respiratory and intestinal infections. Official general data on neonatal nosocomial infections in Bulgaria are available, but without distinguishing the types of infections and their frequency in physiological neonatology sectors from those in intensive neonatology sectors. This makes our NICU-focused data more difficult to compare with official national data.

The infections by gender are almost equally prevalent (53.85% females vs. 46.15% males). Males are associated with more frequent hospitalizations and a higher risk of developing HAI, as reported in the literature[17]. However, a small number of studies have found a higher prevalence in females[18,19]. Gender, according to Tavora et al.[12], is a factor that raises concerns about the risk of HAI.

The most commonly discussed risk factors for the development of HAI in the literature are birth weight and gestational age[12,20,21]. Preterm infants weighing less than 2,500 grams at birth are more likely to develop bloodstream infections. In the 13 patients studied, we calculated a mean birth weight of 2735.38±1120.644 grams and a mean gestational age of 36.3±4.96 weeks. These findings differ from the literature, most studies focusing mainly on premature newborns with very low birth weight. In our study, the higher share is of neonates with a birth weight above 2,500 grams (n=8, 61.5%) and this can explain the different findings regarding birth weight and gestational age.

The average time to the onset of bloodstream infection of 8.92 days was slightly shorter than in other studies: a study from Canada reported 15-19 days to diagnosis[22], 15-18 days in South Korea[23] and 17±14 days in South America[24]. The difference may be explained by the different structure/populations of the studied neonates in relation to the weight/degree of prematurity. The onset of sepsis in and after the 7th day postpartum is classified as late-onset sepsis, as were most cases in our study, and is commonly associated with the use of vascular catheters, mainly CVC. It is especially common in very-low-birth weight (< 1500 g) infants, in whom its occurrence increases the hospitalization duration by 19 days[5].

In neonates with sepsis, CVC or UVC were used for an average of 10 days, whereas the use of PVC was necessary for a significantly longer period, 43.83±21.66 days. The standardization of the CVC placement and maintenance procedure are strategies being discussed for dealing with catheter-associated infections. Some authors consider that these measures would reduce the risk of bloodstream infections by 50%[25].

The length of the hospital stay is another factor that must be considered. Several studies have found that patients with HAI, including those with a bloodstream infection, have a longer duration of hospitalization than those without such an infection[5]. In our study, there were 426 patient days in the 13 newborns who developed bloodstream infections. The average length of stay in the NICU for patients with sepsis was 32.77±20.97 days. Compared to the mean stay duration registered in patients without HAI (12.12±9.16 days) in the same NICU, patients with blood infection have approximately three times longer hospital stay than patients without HAI, demonstrating unequivocally the need for a longer hospitalization of patients whose overall condition is aggravated by this type of infection. Other factors, such as the underlying illness and the type of treatment, may also impact the length of hospital stay.

Temperature instability is an important symptom of possible neonatal infection[26]. This was reported in 8 (61.54%) of bloodstream infection patients. The same proportion of neonates (61.54%) were diagnosed with respiratory disorders. This can be explained by the fact that 8 (64.15%) of these neonates had respiratory pathology at birth or during the perinatal period.

Increased C-reactive protein (CRP) levels are used as a marker of infection, including sepsis[27], and were reported in 84.61% (n=11) of our patients. The average CRP value was 32 mg/dL. CRP has a sensitivity of 65.6% and a specificity of 78% for the diagnosis of neonatal sepsis[28].

The percentage of patients with thrombocytopenia was 38.46% (n=5). Furuichi et al. reported that low platelet counts may indicate catheter-associated blood infection[29].

Coagulase (-) Staphylococcus spp. is recognized as a leading pathogen in bloodstream infections,

particularly those associated with the presence of a CVC or PVC[5,30]. These microorganisms are highly resistant in the environment and can colonize the staff, devices in the wards and neonates admitted in NICU, hence they are a frequent cause of mainly late neonatal infections[31]. Gram-negative microorganisms have been identified as the most common isolates in bloodstream infections in developing countries[32]. The high resistance of *Coagulase (-) Staphylococcus* to Ampicillin and Gentamicin is notable. This can be explained by the frequent use of antibiotics as empirical therapy. The empirical treatment with ampicillin and aminoglycoside is aimed at covering the most common causes of early neonatal sepsis (*Escherichia coli*, *Listeria monocytogenes*, *Streptococcus agalactiae*). The World Health Organization also recommends these two antibiotics as first-line therapy in suspected early or late-onset sepsis[33]. A meta-analysis reported that empiric therapy of neonates with HAI with ampicillin and gentamicin resulted in an increased risk of colonization and HAI caused by extended spectrum beta-lactamases – producing Gram-negative bacteria[34]. Sensitivity to chloramphenicol, linezolid and teicoplanin is fully preserved. In our study, vancomycin sensitivity was found in 75% of all isolates, which is consistent with the findings of other researchers[35].

Limitations of the study

The main limitation of our study is the small number of neonates with catheter-associated bloodstream infections and the lack of a control group to compare the characteristics of the studied neonates. In addition, this study was conducted in only one hospital. Ideally, sampling across other NICUs in Bulgaria would have supported our findings.

Conclusions

In our study, CABSI were the second most common HAI in the NICU. Neonates with this nosocomial infection required a longer hospital stay and more invasive devices. The leading pathogens were Gram-positive flora, and *Coagulase-negative Staphylococcus* was the main main causative agent. Future interventions should focus on developing training programs in infection prevention and control for nurses, midwives and neonatologists, and introduction of bundles for prevention of CABSI.

Authors contributions

V.R conceived the original draft preparation. V.R, A.K., M.K. R.R, were responsible for conception and design of the study. V.R. Y.K. were responsible for the collection of data. All authors contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article "

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the legal representatives of patients included in the study."

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