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RESEARCH ARTICLE

Age <18 years, malnutrition and immunosupression therapy: Risk factors for bloodstream infection caused by *Coagulase Negative Staphylococci* (CoNS)

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ABSTRACT

Most blood culture contaminants are *Coagulase-Negative Staphylococci* (CoNS), which are also the leading cause of nosocomial bloodstream infections. To date, no research in Indonesia has analyzed the potential causes of a CoNS infection in the bloodstream. The goal of this research was to better understand who is at risk for developing a CONS-related bloodstream infection while in a hospital setting. Secondary data from the CONS blood culture results at Dr. Kariadi Hospital Semarang were used in this retrospective cross-sectional study conducted between January 1 and December 31, 2016. The Vitek-2 Compact System (Biomerieux, USA) and the Kirby Bauer method (Clinical & Laboratory Standards Institute (CLSI) of the USA) were used for the antibiotic identification and sensitivity testing, respectively. Multivariate with multiple logistic regressions and the Chi-Square test for categorical variables were used in the analysis. Among the study's 272 participants, 158 (58.1%) developed CONS-related bloodstream infections. Risk factors for central nervous system (CNS) bloodstream infection in 18-year-olds include preterm birth, low birth weight (LBW), compromised immunity, malnutrition, immunosuppressive therapy, and peripheral intravenous use. Age >=18, malnutrition, and immunosuppression therapy all ranked high as risk factors in a multivariate analysis. Risk factors for CONS-causing bloodstream infections in people aged 18 include malnutrition and immunosuppressant therapy.

1. Introduction

Data from intensive care units shows that 36% of all blood cultures were positive for *Coagulase-Negative Staphylococci* (CoNS) due to the prevalence of nosocomial bloodstream infections. 31% of cases of nosocomial bloodstream infections were found to be due to CONS, according to another study (Nguyen *et al.*, 2017). Using the criteria of systemic inflammatory response syndrome (SIRS) in conjunction with the insertion of a central venous catheter (CVC) or not has been the subject of extensive research in developed countries, with results showing a higher level of sensitivity and specificity compared to the CDC's criteria for differentiating between CoNS pathogens and contaminants (Elzi *et al.*, 2012). There has been no research into the causes of CoNS-related bloodstream infections in Indonesia.

Coagulase-negative Nosocomial bloodstream infections are typically caused by staphylococci (CoNS), which are also the most common contaminant in blood cultures (Becke *et al.*, 2014). Globally, but especially in low-income regions, an increase in illness and death is attributed to nosocomial infections, or those contracted from medical care. The term "nosocomial infection" refers to any infection acquired by a patient while in a

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hospital and is often associated with the implantation of medical equipment (Dudeck *et al*., 2013). Additionally, early prosthetic valve infective endocarditis (PVIE), vascular device infections, ventriculoperitoneal shunt (VP), urinary tract infections (UTIs), and sepsis have all been linked to CoNS (Becker *et al*., 2014). Clinical relevance of blood culture CONS isolates in critically ill adults: a systematic review and meta-analysis (Elzi *et al*., 2012). Blood culture positivity time, positive blood culture vial count, positive blood culture set count, species purity, and the presence of sepsis symptoms have all been used to distinguish between contamination and pathogen infections (Kirn and Weinstein, 2013). The epidemiology of CONS bacteremia among stable patients has been discussed in several reports. Most of the published information on the complications of bacteremia is from studies of neonatal and pediatric patients, while reports of cases in adults treated in the ICU are uncommon (Marchant *et al*., 2013). Considering the foregoing, the purpose of this study is to identify the factors that increase the risk of bloodstream infections caused by CoNS, which will aid clinicians in determining whether the infection is actually caused by CoNS as the primary pathogen and not just contamination.

2. Materials and Methods

2.1. Research design

This study is a retrospective cross-sectional analysis of secondary data from patients admitted to Dr. Kariadi Hospital Semarang between January 1 and December 31, 2016. This research was given ethical clearance by the Medical Research Ethics Commission (KEPK) of the Faculty of Medicine at Jenderal Soedirman University / RSUP Dr. Kariadi Semarang (approval number 112/EC/FK-RSDK/III/2018).

The minimum number of samples is 82, and this was determined using the single sample formula for cross-sectional studies. The sampling strategy employed here is purely random. One CONS-positive blood culture vial within 5 days and full supporting data met the inclusion criteria for this study (clinical and laboratory). Identification examination and antibiotic sensitivity test using the Vitek-2 Compact System (Biomerieux, USA) and the Kirby Bauer Method (Clinical & Laboratory Standards Institute (CLSI), USA). Inadequate or missing information in the medical records will prevent participation in the study.

2.2. Analysis of Antibiotic Sensitivity

2.2.1 Vitek-2 Compact System (Biomerieux, USA) (Biomerieux, USA)

An advanced colorimetric and turbidimetric system, this instrument is the most recent iteration of Vitek-2 technology used for identifying and testing the sensitivity of microorganisms to various antimicrobials. Thus, allowing the results of identification and antimicrobial sensitivity to be completed within 5–8 hours. With the most up-to-date technology, the identification and sensitivity of antibiotics can be obtained in just 3 stages, with results validated and interpreted according to CLSI international standards. Inoculum must be prepared, and its turbidity standardized, data must be entered using a barcode system, and finally the card must be inserted into the instrument. And the tool will handle everything from inoculation to incubation to reading to validation to interpreting results automatically. Each Antimicrobial Susceptibility Testing (AST) card contains 16–20 different antimicrobials at varying concentrations; the choice of AST cards is tailored to the type of bacteria; and for antifungals, one card contains 4 different antifungals at varying concentrations. It is possible to link this test's outcomes squarely to the LIS as well (Laboratory Information System). Nothing but the Vitek-2 card, and the sterile saline solution are needed as reagents.

2.2.2. Kirby Bauer

The Kirby Bauer method (CLSI, USA) is a way to determine antibiotic sensitivity for bacteria. The size of the inhibition zone is an indicator of how susceptible a bacterium is to an antibiotic. If you want to know if bacteria are resistant to a certain antibiotic, you need to know their diameter relative to a reference standard. The Kirby-Bauer method for testing antibiotic efficacy entails the following steps: (1)

Cotton swabs can be used to collect bacteria cultures by dipping them in the solution and pressing them against the tube's side; (2) Diffuse it throughout the Mueller-Hinton cup's entire top, (3) The plate needs to sit for 5 min, (4) Antibiotic solutions of a certain concentration are dipped onto discs of paper, (5) Take off, let the excess liquid drain for a second, and then set the disc paper on top of the agar, (6) Use of tweezers ensures a secure bond between the disc paper and the agar surface, (7) 24-48 hours of incubation at 37 degrees Celsius, (8) Determine the diameter of the inhibition zone in millimetres and check it against the CLSI table.

2.3. Analytical Statistics

Continuous variables are presented in the form of average values plus standard deviations (SD), and categorical variables are presented in proportions of the number of patients or groups. Chi-Square test for categorical data and Mann-Whitney U test for numerical data constitute bivariate analysis. Analysis

Table 1. Clinical characteristics in 272 patients

Characteristic	Pathogenic CoNS (n = 158)	Nonpathogenic CoNS (n = 114)	Amount (n = 272)	p[a]
SIRS Criteria				
Temperature (Mean ± SD)	37,52 ± 1,07	36,9 ± 0,61	**37,28 ± 0,94**	**0,000****
Respiration (Mean ± SD)	30,86 ± 11,20	24,25 ± 14,89	28,09 ± 13,26	0,000**
Pulse (Mean ± SD)	123,01 ± 25,39	98,85 ± 23,36	112 ± 27,27	0,000**
Leukocyte (Mean ± SD)	16,49 ± 9,31	13,19 ± 7,83	15,11 ± 8,85	0,000**
SOFA Score (Mean ± SD)	4,41± 3,40	2,72 ± 2,78	3,70 ± 3,25	0,000**
SOFA Classification (n %)				0,000**
Sepsis	120 (65,0)	63 (35,0)	183 (100)	
Non-Sepsis	38 (43,8)	51 (56,2)	89 (100)	
APACHE II Score (Mean ± SD)	17,13± 8,01	12,47± 6,83	5,18 ± 7,87	0,000**
Type of Treatment				0,454
Intensive	54 (55,1)	44 (44,9)	98(100)	
Non intensive	104 (59,8)	70 (40,2)	174 (100)	
Duration of Treatment (Mean ± SD), Hari	16,92 ± 13,85	19,24 ± 12,82	17,89 ± 13,45	0,046*
Infection onset (Mean ± SD), days	6,81 ± 7,78	8,16 ± 8,49	7,37 ± 8,10	0,149
Infection duration (Mean ± SD), days	9,95 ± 10,55	11,25 ± 8,57	10,49 ± 9,78	0,021*
Types of infection (n %)				0,528
Nosocomial	91 (56,5)	70 (43,5)	161 (100)	
Community	67 (60,4)	44 (39,6)	111 (100)	
Antibiotic Administration (n, %)				1,000 [b]
Yes	157 (57,9)	114 (42,1)	271 (100)	
No	1 (100)	0	1 (100)	
Duration of Antibiotic therapy (Mean ± SD)	14,77 ± 13,01	14,74 ± 9,91	14,76 ± 11,79	0,386
Number of vials Send (n %)				0,337
1 vial	85 (61,3)	68 (38,7)	153 (100)	
2vials	73 (55,6)	46 (44,4)	119 (100)	
Number of Positive Samples (n %)				0,000*
1 vial	136 (54,4)	114 (45,6)	250 (100)	
2vials	22 (100)	0 (0,0)	22 (100)	
Organism (n, %)				
Staphylococcus haemolyticus	63 (39,9)	43 (37,7)	106 (100)	
Staphylococcus hominis	51 (54,3)	43 (45,7)	94 (100)	
Staphylococcus epidermidis	33 (57,9)	24 (42,1)	57 (100)	
Staphylococcus capitis	6 (3,8)	1 (0,9)	7 (100)	
Staphylococcus warneri	2 (100)	0 (0,0)	2 (100)	

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Characteristic	Pathogenic CoNS (n = 158)	Nonpathogenic CoNS (n = 114)	Amount (n = 272)	p[a]
Staphylococcus saprophyticus	1 (100)	1 (100)	2 (100)	
Staphylococcus lentus	1 (100)	0 (0,0)	1 (100)	
Staphylococcus gallinarum	1 (50)	1 (50)	2 (100)	
Staphylococcus cohnii	0 (0,0)	1 (100)	1 (100)	
Antibiotic Resistance (n %)				0,391
MRCoNS	113 (59,8)	76 (40,2)	189 (100)	
CoNS	45 (54,2)	38 (45,8)	83 (100)	

aUnivariate Analysis, *$p < 0,05$, ** $< 0,0001$

Table 2. Bivariate and multivariate analysis of age, prematurity, low birth weight, immunocompromised and invasive medical devices

Risk Factors	Pathogenic CoNS (n = 158)	Nonpathogenic CoNS (n = 114)	Amount (n = 215)	Bivariate Analysis	Multivariate Analysis		
				p^b	PR (95 % CI)	p^c	PR (95 % CI)
Surgical Procedures (n, %)				0,003	1,411 (1,098 – 1,813)	0,042*	3,711 (1,051 – 13,101)
Surgery	41 (45,6)	49 (54,4)	90 (100)				
Non-Surgery	117 (64,3)	65 (35,7)	182 (100)				
Age Risk (n, %)				0,000	1,661 (1,373 – 2,010)	0,000**	3,992 (1,965 – 8,112)
High risk age	77 (77,8)	22 (22,2)	99 (100)				
Low risk age	81 (46,8)	92 (53,2)	173 (100)				
Prematurity (n, %)				0,002	1,620 (1,349 – 1,946)	0,924	1,088 (0,193 – 6,138)
Yes	18 (90)	2 (10)	20 (100)				
No	140 (55,6)	112 (44,4)	252 (100)				
Low Birth Weight				0,002	1,620 (1,349 – 1,946)		
Yes	18 (90)	2 (10)	20 (100)				
No	140 (55,6)	112 (44,4)	252 (100)				
Immunocompromised				0,003*	1,620 (1,349 – 1,946)	0,69	1,244 (0,426 – 3,634)
Yes	74 (72,5)	28 (27,5)	102 (100)				
No	84 (49,4)	86 (50,6)	170 (100)				
Immunocompromised types							
Malnutrition				0,000**	1,554 (1,296 – 1,864)	0,008*	4,501 (1,480 – 13,690)
Yes	56 (78,9)	15 (21,1)	71 (100)				
No	102 (50,7)	99 (49,3)	201 (100)				
Malignancy				0,292	0,842 (0,602 – 1,177)		
Yes	19 (50)	19 (50)	38 (100)				
No	139 (59,4)	95 (40,6)	234 (100)				
Immunosuppression				0,032*	1,374 (1,095 – 1,725)	0,042*	3,711 (1,051 – 13,101)

Risk Factors	Pathogenic CoNS (n = 158)	Nonpathogenic CoNS (n = 114)	Amount (n = 215)	Bivariate Analysis	Multivariate Analysis		
				p^b	PR (95 % CI)	p^c	PR (95 % CI)
Therapy							
Yes	23 (76,7)	7 (23,3)	30 (100)				
No	135 (55,8)	107 (44,2)	242 (100)				
HIV/AIDS				1	1,150 (0,513 – 2,575)		
Yes	2 (66,7)	1 (33,3)	3 (100)				
No	156 (58,0)	113 (42,0)	269 (100)				
Invasive Medical Devices (n, %)				0,256	0,889 (0,723 – 1,091)		
Invasive Medical Devices > 2	90 (61,2)	57 (38,8)	147 (100)				
Invasive Medical Devices < 2	68 (54,4)	57 (45,6)	125 (100)				
Invasive Medical Devices types (n,%)							
CVC (n, %)				0,000**	0,577 (0,488 – 0,682)	0,001*	0,194 (0,071 – 0,534)
Yes	52 (86,7)	8 (13,3)	60 (100)				
No	106 (50,0)	106 (50,0)	212 (100)				
Peripheral intravenous (n, %)				0,025*	1,480 (1,172 – 1,869)	0,721	0,710 (0,108 – 4,653)
Yes	143 (56,3)	111 (43,7)	254 (100)				
No	15 (83,3)	3 (16,7)	18 (100)				
Drain (n, %)				0,007*	1,719 (1,058 – 2,793)	0,223	1,927 (0,671 – 5,538)
Yes	11 (35,5)	20 (64,5)	31 (100)				
No	147 (61,0)	94 (39,0)	241 (100)				
Endotracheal Tube (n, %)				0,014*	1,216 (0,996 – 1,483)	0,537	0,789 (0,373 – 1,672)
Yes	45 (71,4)	18 (28,6)	63 (100)				
No	113 (54,1)	96 (45,9)	209 (100)				
Tracheostomy tube (n, %)				0,175	0,415 (0,360 – 0,478)		
Yes	0 (0,0)	2 (100)	2 (100)				
No	158 (58,5)	112 (41,5)	270 (100)				
Nasogastric tube (NGT)				0,091	0,840 (0,688 – 1,026)		
Yes	73 (64,0)	41 (36,0)	114 (100)				
No	85 (53,8)	73 (46,2)	158 (100)				
Urine Catheter				0,063	1,216 (0,996 – 1,483)		
Yes	95 (54,0)	81 (46,0)	176 (100)				
No	63 (65,6)	33 (34,4)	96 (100)				

[b] *Chi Square Test*, c Multiple Logistic Regression *p <0,05, **p < 0,0001

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of multiple variables by means of logistic regression SPSS version 20 is used for all statistical analysis. The analysis yields a prevalence risk (PR), a probability value (*p* value), and a 95% confidence interval (CI) (CI).

3. Results

During the period 1 January–31December, 2016, 406 isolates of Coagulase-negative Staphylococci were obtained; as many as 134 isolates were issued because the medical record data was incomplete, so the total number that could be analyzed was 272 patients. From these numbers, we can deduce that 158 (58.1%) of the isolates were CNS pathogens and that 114 (41.9%) were CNS non-pathogens. This study of 272 patients' clinical characteristics found that pathogenic and non-pathogenic CoNS differed in terms of the average SIRS criteria components (temperature, respiration, pulse, and leukocytes), SOFA scores, APACHE II scores, treatment duration, and the number of positive samples with $p = 0.001$. (Table 1). Prevalence of blood flow infections caused by CoNS was found to be greater in the high-risk age group, in patients who were premature or had a low birth weight, in patients who were immunocompromised, in patients who were malnourished, in patients who were receiving immunosuppression therapy, and in patients who were receiving a central venous catheter (CVC). This research found no correlation between the presence of CONS and the presence of HIV/AIDS, cancer, or the use of invasive medical devices. Malnutrition (RR = 4.051, $p = 0.008$), immunosuppression therapy (RR = 3.711, $p = 0.042$), and being over the age of 18 all pose substantial risks.

4. Disscussion

Out of the total number of patients surveyed (272), 158 (58.1%) had CoNS-related bloodstream infections. Constant negative pressure (CONS) bloodstream infection risk factors include prematurity, low birth weight, immune system disorders, malnutrition, immunosuppressive therapy, and the use of peripheral intravenous catheters. Multivariate analysis identifies the 18-year-old age group, malnutrition, and immunosuppression therapy as significant risk factors. Previous studies have suggested that neonates are more susceptible to CONS infection than adults due to immature immune systems, particularly the complementary system (Nguyen *et al.*, 2017). In the NICU, GBS and Gram-negative bacteria are common causes of bacteremia in newborns; later, CoNS was identified as a pathogen in critically ill hospitalized infants and preterm infants (Marchant *et al.*, 2013). Infections in neonates at the NICU are typically caused by Gram-positive organisms, specifically *Staphylococcus epidermidis*.

CoNS is the most common microorganism in cases of EOS in both full-term and premature infants (2.4/1,000 and 2.5/1,000 treatments, respectively) (Bizzarro *et al.*, 2015). Genotyping research has demonstrated that *S. epidermidis* and *S. haemolyticus* strains colonise newborns' gastrointestinal tracts; these bacteria are major contributors to the development of LOS in premature infants (Soeorg *et al.*, 2013). Another study confirmed that CONS is a leading cause of LOS in the neonatal period for infants with low birth weight, especially for those with very low birth weight (VLBW). Infants with a CONS infection have a higher risk of neonatal morbidity, longer hospital stays, and even death (De Oliveira *et al.*, 2012). According to prospective population-based observational studies of NS, CONS accounted for 13.6% of all infections, with a rate of 0.67 per 1,000 live births. VLBW (1,500 g at birth), low gestational age, a history of intravascular catheters, and prolonged parenteral nutrition are all risk factors for infection I. CoNS infection, which is more commonly associated with *S. aureus* infection (Ozkan *et al.*, 2014).

In immunocompromised patients, CNS pathogens tend to thrive. In immunocompetent young adults without risk factors, bloodstream infections caused by CoNS are uncommon. Malnutrition, cancer, immunosuppression treatment, and the human immunodeficiency virus (HIV) were all considered as potential causes of immunosuppression. Studies have shown that anorexia and infectious diseases are common contributors to severe acute malnutrition (SAM), which is the result of a short period of nutritional deficits. In children with SAM, comorbidities like diarrhea, pneumonia, malaria, and a weakened immune system continue to be the leading cause of death. The high mortality rate associated with complications necessitates hospitalization for children. Children who are malnourished have a higher risk of developing bacterial infections like bacteremia, UTIs, diarrhea, and pneumonia. The skin flora consists primarily of CoNS, and severe malnutrition can cause bacteremia by disrupting the skin's normal defense barrier and allowing CoNS to enter the bloodstream. When it comes to critically ill children and immune disorders, NS is a well-established contributor to sepsis (Jones *et al.*, 2014).

Epidermidis is the most common cause of septicemia, occurring in about 20% to 40% of patients and most commonly in those receiving immunosuppressive therapy or developing neutropenia because of chemotherapy. More than 40% of cases were caused by pathogenic CONS found in patients with hematological malignancies and solid tumors,

according to a multicenter study that analyzed the etiology of 1,051 bacterial events or episodes in 782 cancer patients. CONS was found to be the most common pathogen causing bloodstream infections in patients with hematological malignancies in a separate study involving 54 hospitals. Chemotherapy-induced neutropenia, skin or mucosal abnormalities, and prolonged central venous catheter use have all been linked to an increased risk of CoNS bacteremia in patients with hematological malignancies. Hematology patients with neutropenia may develop a nosocomial bloodstream infection due to CONS, with *S. epidermidis* as the most common causative organism (Montassier *et al*., 2013). Infections caused by pathogenic CONS are less common in patients undergoing surgery, so the incidence of such infections is not heightened by the operation itself. Patients with intravenous or surgical catheters were found to be risk factors for CONS bloodstream infection at a p 0.05 in another study that differentiated between pathogenic CONS and non-pathogenic CONS using clinical criteria (Karakullukçu *et al.*, 2017).

The analysis showed no meaningful association between the use of invasive medical devices and the development of pathogenic CONS. Patients with CONS who use CVCs do not have a higher risk of developing a bloodstream infection. Patients receiving peripheral intravenous were more likely to develop CONS-related bloodstream infections than those who did not. Bloodstream infections caused by CONS are not more likely when drains and ET are used. Many studies have found that 30–60% of all catheter-related bloodstream infections are caused by bacteria found in the central nervous system. These results are corroborated by research showing that patients with an intravenous catheter or undergoing surgery have an increased risk of contracting a bloodstream infection due to CONS ($p < 0.05$; Karakullukçu *et al*., 2017). This was determined by using clinical criteria to differentiate between pathogenic and non-pathogenic CONS.

All variables from the $p < 0.05$ bivariate analysis were subjected to a multivariate analysis, the results of which are shown in Table 2. The following factors increase the likelihood that a case of pathogenic CoNS will develop age at maximum vulnerability (PR = 3.992, p <0.0001). According to CONS 3,992, the incidence of bloodstream infections was greater in the high-risk age group than in the low-risk age group. undernourishment (OR = 4.051, p = 0.008). Bloodstream infections, as measured by CoNS 4,051, were more common in malnourished patients than in healthy ones. Antibody-destroying drugs (OR = 3.711, p = 0.042) Patients on immunosuppression therapy had a higher rate of bloodstream infections compared to those on a control group's non-immunosuppression therapy, as measured by CONS 3,711. The above-mentioned risk factors should be planned for in advance to lower the incidence of bloodstream infections by CONS, with prompt and appropriate clinical treatment to resolve sepsis as soon as possible. This study's limitations stem from its retrospective nature, which necessitated an examination of each patient's medical file. Because researchers can't speak with patients or observe their conditions, the retrospective method isn't ideal for assessing the factors that contribute to bloodstream infections caused by pathogenic CONS. There has never been a study conducted on CONS-related bloodstream infections before, and this one is the first of its kind in Indonesia. This study's data were collected from just one major medical center, so its findings cannot be generalized to the population at large. Potentially, future studies will need to conduct research at multiple centers.

5. Conclusions

The incidence of bloodstream infections due to CONS in this study was 58.1%, quite high compared to other studies, which ranged from 10 to 30%. Special attention is needed to prevent and treat CONS infection at RSUP, says Dr. Kariadi. The age group of 18 years has an increased prevalence of bloodstream infections. Cases of infection of the bloodstream increase with the use of immunosuppression therapy, malnutrition, and the use of peripheral intravenous lines.

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