CASE REPORT

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The relationship between bacterial types and antibiotic resistance with the clinical outcomes of sepsis patients in Pediatric Intensive Care Unit at Sanglah Hospital Denpasar, Bali-Indonesia

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ABSTRACT

Background: Sepsis in children could significantly increase the morbidity and mortality rates particularly in the Pediatric Intensive Care Unit (PICU). Moreover, the prevalence of antibiotic resistance is continuously increasing around the world mainly caused by uncontrolled used of antibiotic. Henceforth, this study aimed to determine the relationship between bacterial type and the resistance with clinical outcome of sepsis patients in PICU.

Methods: An observational analytic retrospective cohort study using medical record data from January 2015-April 2017 was conducted. All subjects were sepsis patients with positive blood cultures treated at PICU Sanglah Hospital. Factors related to mortality and relative risk (RR) were analyzed using Chi-Square Test with a significance value of $p < 0.05$ with 95% confidence interval (CI).

Results: 75 subjects met the inclusion criteria, but only 63 subjects with complete data were enrolled. The gram-negative and MDR bacteria types were detected in 31 (49%) subjects and 33 (52.4%) subjects respectively. The number of deaths was 29 (46%). The most common types of gram-negative bacteria were *Pseudomonas aeruginosa* (16%) followed by gram-positive *Staphylococcus hominis* (25%). The most common multi-drug resistant (MDR) bacteria were *Staphylococcus hominis*. The presence of MDR bacteria significantly increase the mortality ($p = 0.015$, RR 2.02, 95% CI: 1.096-3.725), whereas gram-negative had no significant mortality impact ($p = 0.891$: RR 0.96; 95% CI: 0.564- 1.645). Compared to non-MDR bacteria, most MDR related mortality occurred during the first 10 days.

Conclusion: MDR bacteria significantly increased the mortality rates in pediatric patient treated in PICU compared to non-MDR ones.

Keywords: Sepsis, Bacteria Types, Multidrug Resistance, Clinical Outcomes, PICU

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INTRODUCTION

Sepsis is an organ dysfunction caused by dysregulation of the immune system against infection.[1] Sepsis remains as one of the leading causes of mortality and morbidity in developing countries. The mortality rate of sepsis in the pediatric intensive care unit (PICU) is 50% higher for developing countries compared with developed countries. WHO data show that 80% of deaths in children under 4 years old were associated with sepsis. The clinical outcomes of sepsis patients in PICU are influenced by various factors such as diagnosis at admission, patient demographic status, the presence of comorbidities and hospital infrastructure.[2] Other factors that are also currently associated with mortality among sepsis patients includes the type of bacteria and resistance to antibiotics.

The gram-negative bacteria are the most common causes of septic associated death mainly from septic shock. The infection could lead to a more severe and lethal systemic response than a gram-positive bacterial infection.[3,4] However, several studies still showed conflicting results regarding the association between bacterial type and mortality rate. A study conducted by Armenian et al. in 2005 showed that gram-negative bacterial infection had 5.67 times higher mortality rate compared with gram-positive bacteria.[5] In contrast, a study conducted by Sogaard et.al[22] in 2011 found that gram-negative bacteria had no effect on the mortality rates among sepsis patients. The difference in structure between gram-negative and gram-positive bacteria is one of the causes that underly the severity of the inflammatory response.[3,4] The outer membrane is a component possessed only by gram-negative bacteria and plays an important role in the lethal inflammatory response of sepsis. Lipopolysaccharide (LPS) is an endotoxin that makes up nearly 70% of outer membranes in gram-negative bacteria.[4,6,7] Lipid-A is part of the LPS that trigger macrophages to produce pro-inflammatory TNF-α and

IL1β cytokines. TNF-α will then induce the expression of other pro-inflammatory cytokines such as IL-10 and IL-4. These inflammatory responses play a pivotal role in the pathogenesis of shock in sepsis.[7] In contrast to exotoxin, the endotoxin levels will continue to rise along with the increase of cell division and cell death which keep the inflammatory response despite the increased rate of bacterial elimination by antibiotics.[8] Another component of the outer membrane which also contribute to the septic shock is porin. Porin has the potential to stimulate the release of pro-inflammatory cytokines such as IL-1, IL-4, IL-6, IL-8, TNF-α, and INN-γ which would contribute greatly to the development of sepsis.[9]

Another factor that is also associated with the high mortality risk in sepsis is multidrug-resistant bacteria (MDR) infection. The emergence of antibiotic resistant pathogenic microorganisms against certain types of antibiotics greatly complicates the treatment process and lead to several fatal consequences. The main cause of resistance is the widespread and irrational use of antibiotics (short duration of administration, inadequate doses, and incorrect initial diagnosis) in the hospital or community. Sepsis caused by gram-positive or gram-negative MDR may result in the prolonged illness, increased mortality rate as well as the length of hospitalization.[10-12] A study conducted by Folgori et al[23] in 2014 found that MDR was associated with 4.26 times increase in mortality risk but the study only carried out in subjects with gram-negative infections. In addition, currently, there is no study on antibiotic resistance associated mortality rate that involves gram-positive and gram-negative bacteria.

Due to lack of information about MDR bacteria and its associated mortality and morbidity in Indonesia, the authors aimed to determine the relationship between bacterial types and antibiotic resistance status with the clinical outcomes of sepsis patient treated in PICU.

METHODS

Study Design and Subject Selection

This study was a retrospective cohort design using medical record data from January 2015-April 2017. The data collected in the form of secondary data and obtained from medical records of patients treated at PICU Sanglah Hospital.

The samples of this study were all pediatric patients treated at PICU Sanglah Hospital and had been selected according to the inclusion and exclusion criteria. The inclusion criterion includes the diagnosis of sepsis according to the medical record with a positive blood culture on one or two sides. Those with incomplete medical records, contaminated positive blood culture, two types of bacteria detected from one blood culture (gram-negative and positive) in one period of blood culture or one period of treatment at PICU, and cardiac abnormalities. According to statistical formula, the minimum sample size required in this study was 28 subjects for each group based on the previous methods.[5,14]

Data and Variables

Data obtained in this study included: age, sex, total score of PRISM III, suspicion of primary infection, source of infection, type of bacteria, MDR, clinical outcome and length of stay. The operational definitions of variables which measured or observed in this study are described below:

1. Age was obtained from the difference between the date when the subject hospitalized with the date of birth, which then divided into ≤ 12 months and > 12 months.
2. Sex was determined by phenotypic appearance which differentiated into men and women.
3. The diagnosis of Sepsis was established if there was at least 2 signs of inflammatory response with positive blood culture. Inflammatory responses including fever, tachycardia or bradycardia, tachypnea, leukopenia or leukocytosis. Organ dysfunction was added to the diagnosis of sepsis after 2016 which could be assessed by PELOD 2. The diagnosis of sepsis was obtained from medical record data.
4. PRISM III is a score used in predicting patient mortality in PICU which performed during the first 24 hours after treated in PICU.
5. Suspicion of primary source of infection is the location where the infection that underlies the sepsis. Primary infection sites are categorized into central nervous system, respiratory system, gastrointestinal tract, post-surgery, and others.
6. The source of infection is categorized into community and nosocomial. Community infection is an infection or signs of infection that observed when a patient admitted to the hospital. Nosocomial infection is an infection that occurred after ± 72 hours of hospitalization with no evidence of occurrence prior to hospitalization.
7. The type of bacteria is determined from the blood culture examination on one or two sides and differentiated into gram-negative and gram-positive. The bacteria type is strongly suspected as the causative agent of the infection and not as a contaminant.

8. Antibiotic resistance is a condition of bacterial resistance against antibiotics and differentiated into MDR and non-MDR. It is referred as Multidrug-resistant (MDR) when the resistance occurred against three or more classes of antibiotic whereas the resistance to fewer than three types of antibiotics was classified as non-MDR.
9. Clinical outcomes are the conditions of subjects when discharged from the hospital as seen from the medical record which divided into life and death.
10. The length of stay is calculated in days based on the difference between the PICU admission date and when the patients were discharged from PICU. If the initial diagnosis of admission to PICU is not sepsis and changed into suspected sepsis during the course of treatment, then the length of hospitalization is calculated from the date of the sepsis being suspected and blood culture collection until discharged from PICU.

Statistical Analysis

Subject characteristics data were presented descriptively in the form of tables, figures, and narratives. The bivariate analysis was performed to assess the relationship between the independent and dependent variables by using *Chi-Square* test in order to obtain the value of relative risk (RR). The entire statistical tests were performed by using SPSS ver. 22 where 95% CI and p-values <0.05 were considered as significant.

RESULTS

75 patients were found to have sepsis from January 2015 - April 2017, but only 63 had complete medical record data with 29 (46%) patients died, and 34 (54%) were alive regarding the clinical outcome. 31 (49.2%) subjects were found to be infected by gram-negative bacteria while 32 (50.8%) were infected by gram-positive. Furthermore, 33 (52.4%) subjects were found to have infection from MDR bacteria.

Most of the subjects were ≤12 months and predominantly male 38 (60.3%). According to the focus of infection, more than half of subject had suspected infection in the respiratory system (34 subjects; 54%), and most infection was community acquired (46 subjects; 73%). The average score of PRISM 3 was 8.54 and the average length of stay in PICU about 10 days (Table 1).

The most common gram-negative species were *Pseudomonas aeruginosa* which was found

Table 1 Subject Characteristics

Variable	n = 63
Age:	
≤ 12 months, n (%)	41 (65.1%)
> 12 months, n (%)	22 (34.9%)
Sex:	
Male, n (%)	38 (60.3%)
Female, n (%)	25 (39.7%)
Suspicion of primary infection site:	
CNS, n (%)	11 (17.5%)
Respiratory system, n (%)	34 (54.0%
Gastrointestinal system, n (%)	4 (6.3%)
Post-surgery, n (%)	4 (6.3%)
Others, n (%)	10 (15.9%)
Source of Infection:	
Community, n (%)	46 (73.0%)
Nosocomial, n (%)	17 (27.0%)
PRISM 3 scores, mean (SD)	8.5 (5.3)
Type of Bacteria:	
Gram-negative, n (%)	31 (49.2%)
Gram-positive, n (%)	32 (50.8%)
Bacterial Resistance:	
MDR, n (%)	33 (52.4%)
Not-MDR, n (%)	30 (47.6%)
Length of Stay (Days), median (min-max)	10 (1-23)

Table 2 MDR Bacterial Isolates collected during the course of the study

Type of MDR Bacteria	n =33
Staphylococcus hominis	6
Staphylococcus haemolyticus	3
Pseudomonas aeruginosa	3
Achromobacter xylosoxidans	3
Others CoNS	2
Enterobacter cloacae	2
Klebsiella pneumoniae	2
Acinetobacter baumannii	2
Staphylococcus cohnii	1
Aerococcus viridans	1
Enterococcus faecalis	1
Staphylococcus saprophyticus	1
Elizabethkingia meningoseptica	1
Salmonella ssp	1
Salmonella typhi	1
Pseudomonas stutzeri	1
Rotellaornithynolytica	1
Aeromonas hydrophilia	1

Table 3 The association between bacteria's types and antibiotic resistance with clinical outcome of sepsis patients

Variable	Clinical Outcome		RR	CI 95%	*p-value*
	Died	Live			
Types of Bacteria:					
Gram-negative	14 (45.2%)	17 (54.8%)	0.96	0.564-1.645	0.891
Gram-positive	15 (46.9%)	17 (53.1%)			
Resistance status:					
MDR	20 (60.6%)	13 (39.4%)	2.02	1.096- 3.725	0.015
Non-MDR	9 (30.0%)	21 (70.0%)			

RR = *Relative Risk*; CI = *confidence interval*

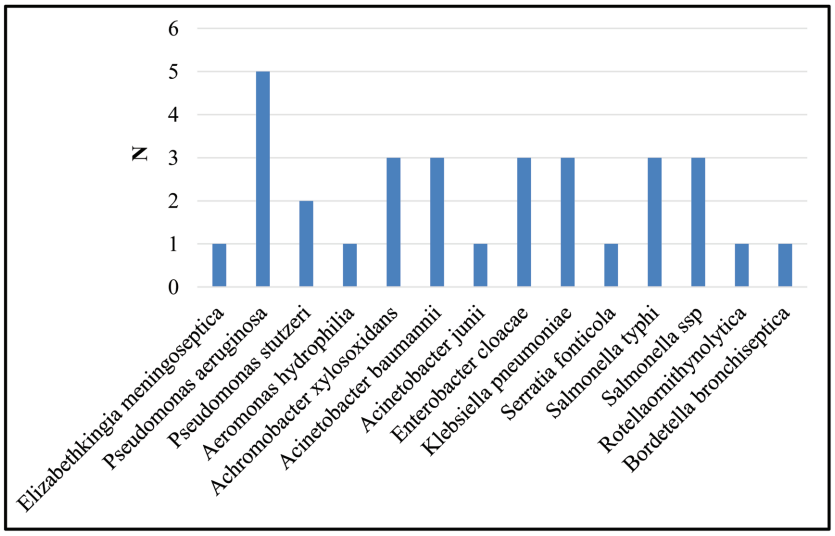

Figure 1 The species and quantity of gram-negative bacteria found in the study

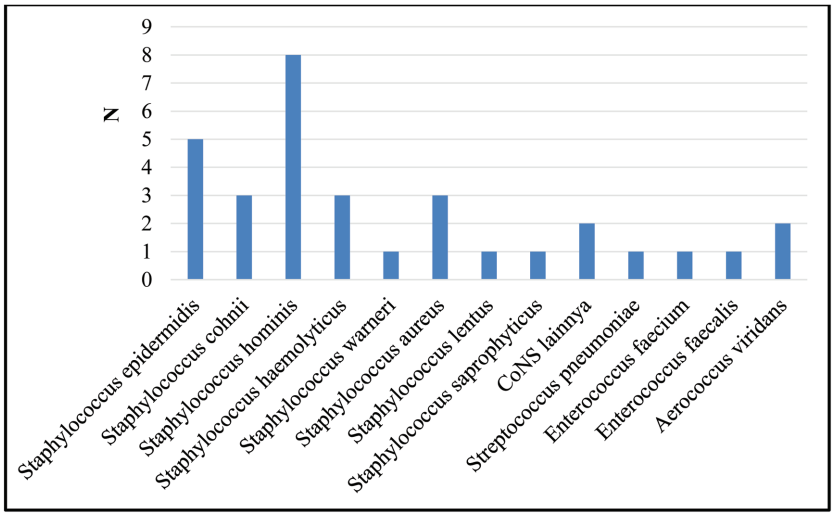

Figure 2 The species and quantity of gram-positive bacteria found in the study

in 5 (16%) subjects, whereas the most common gram-positive species were *Staphylococcus hominis* which affect 8 (25%) subjects. (Figure 1 and 2). In addition, the most common type of MDR bacterial from the entire culture is *Staphylococcus hominis* (Table 2). From 6 isolates of the MDR's,

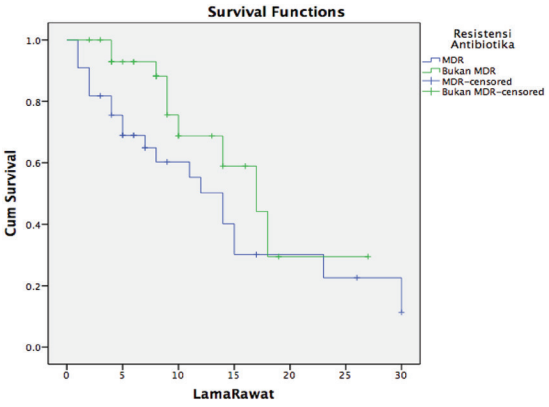

Figure 4 Kaplan Meier's Curve showing the pattern of mortality in MDR and non-MDR group

Staphylococcus hominis was found to be 100% sensitive to gentamicin, vancomycin, and tigecycline. The bacteria were the more resistant to clindamycin, ampicillin-sulbactam, and cefazolin.

According to bivariate analysis, it was found that only the MDR variable increased the risk of mortality in sepsis patients treated in PICU ($p < 0.05$) whereas the association with gram-negative infection was found to be not statistically significant ($p > 0.05$). The results are presented in Table 3.

Kaplan Meier's curve shows that the mortality in sepsis caused by MDR occurs more frequently in the first 10 days than the non-MDR group. After 15 days of treatment, the mortality rates between MDR and non-MDR was found to be equal (Figure 4).

DISCUSSION

Sepsis is a life-threatening organ dysfunction resulting from infection-related immune dysregulation. The incidence of sepsis is higher in neonates and infants compared with age >1-18 years.[1] It is consistent with the characteristic data in this study which suggest that 65.1% subjects with sepsis were aged ≤12 months. Other characteristic data showed that most subjects are male with most suspected infection sites were from the respiratory system. These results are similar to a study conducted by

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Supit et al[15] in 2016 where 61% subjects with sepsis were male. Study on *Sepsis Prevalence Outcomes and Therapies* (SPROUT) in 2015 also showed similar results where most infections originated from the respiratory system.

The source of sepsis infection is primarily acquired from the community. There are only 27% were considered as nosocomial infections. We used PRISM 3 to predict the mortality of the patients. PRISM 3 is a score that can be used in predicting the occurrence of mortality when performed within the first 24 hours of entering the PICU. Patients with PRISM score above 80 has a mortality rate of 97%.[17]

The most common species of gram-negative bacteria found in this study was *Pseudomonas aeruginosa*. A similar result was found in a systematic review conducted by Berezin et al[18] in 2014 which showed that *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Escherichia colli* as the most common gram-negative species of sepsis in PICU. *Pseudomonas aeruginosa* is a pathogen which often found in nosocomial infection and rarely found in the community-acquired infection.[19] On the other hand, the most common gram-positive species found in this study were *Coagulase negative staphylococci* (CoNS) such as *Staphylococcus hominis* and *Staphylococcus epidermidis*. These bacteria are more likely to be contaminants but may also be pathogenic in patient with several risk factors such as infants, immunodeficiency conditions, and history of invasive procedure.[20,21] Bacterial growth that occurred within the first 48 hours in culture, as well as their clinical sepsis diagnosis, become a consideration that the bacteria are not contaminants.

Several factors influence the clinical outcomes of sepsis patients in PICU. One of them is a gram-negative bacterial infection. The mortality rate of patients with sepsis caused by gram-negative bacteria could reach 20-50%, while the gram-positive ones only ranged between 10-20%.[19] A study conducted by Armenian et al[5] in 2005 showed that gram-negative bacteria could increase the mortality rate as much as 5.67 times compared with gram-positive bacterial infection. In contrast, a study conducted by Sogaard et al. in 2011 found that gram-negative bacteria did not increase the mortality rates (RR 0.8; CI 95% 0.5-1.1). These previous studies are consistent with our study which indicates that the gram-negative did not increase the risk of death in sepsis patients treated in PICU (p: 0.891; RR: 0.96; CI 95%: 0.564-1.645). The differences in the study results with the hypothesis could be due to the changes in the virulence of gram-positive bacteria. The transformations that occurred in gram-positive bacteria may result in a more virulent strain.

An increasing number of microbial resistance to certain types of antibiotics recently become a global issue due to its negative effects on the clinical outcome of the hospitalized patient. Other than increasing the hospital costs, these conditions may enhance the length of care and the number of mortality.[23] According to results of this study, it appears that MDR could increase the risk of death to about twice as much as non-MDR in sepsis patients treated in PICU (p-value: 0.015; RR 0.96; CI 95% 0.564-1.645). The mortality rate is more common in the first 10 days of infection compared to non-MDR group. A study conducted by Folgori et al. in 2014 reported that MDR increased the risk of death by 4.26 times, but the study only evaluates gram-negative bacterial infection. Similar results were also obtained by Zilberberg et al[24] who reported that MDR infection results in 11 times higher mortality rate in the adult sepsis patients at intensive care unit.

The most common type of MDR bacteria in this study was *Staphylococcus hominis*. Since it was first discovered in 1998, the bacteria are more commonly known as contaminants. From 2002 until recently, *Staphylococcus hominis* began to be found as pathogenic bacteria commonly found as the cause of sepsis and many of which were MDR. A study by Cekovska et al[25] showed that *Staphylococcus hominis* still have a 100% sensitivity to vancomycin and tigecycline, whereas the most others were resistant to penicillin, oxacillin, erythromycin, and clindamycin. These results were similar to this study where the bacteria still have 100% sensitivity to vancomycin and tigecycline but not to gentamicin, while the others had resistance against clindamycin, ampicillin-sulbactam, and cefazolin.

Considering the magnitude of the effect of MDR on the mortality of sepsis patients in PICU, several strategies may be undertaken to prevent the occurrence of MDR. These strategies include restriction and regulation of antibiotic usage, development of guidelines for antibiotics use, administration of combination therapy instead of monotherapy, implementing a regular rotation system of antimicrobials (antimicrobial cycling), avoiding prolonged use of antibiotics as well as optimizing the way antibiotics are provided according to the pharmacokinetics and pharmacodynamics of the drug.[10] Preventing the spread of MDR bacteria, particularly in hospitals is also very important. One of them is by applying the system of prevention and control of nosocomial infections. In addition, it is important to know the type of bacterias that have MDR and the antibiotics that are effective against them, to ensure optimal and effective administration of antibiotic and, thus, improving the clinical outcome.

However, this study has indeed had a limitation that needs to be considered in which the diagnosis of sepsis in the medical record prior to 2016 did not have PELOD 2 score as in 2017, so it possesses a risk of selection bias. Further study is needed using prospective study designs by analyzing other factors that may also affect the mortality of PICU patients.

CONCLUSION

Multidrug-resistant was proven as the risk factor of mortality in septic patients treated in PICU, while the gram-negative bacteria were not significantly associated with mortality.

ETHIC APPROVAL

The ethical clearance is provided by the Research Ethics Committee, Faculty of Medicine Udayana University, Sanglah Hospital (No:1309/UN.14.2/KEP/2017).

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