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Original Article

Risk factors of late onset sepsis caused by extended spectrum β-lactamase - producing bacteria in preterm infants

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Abstract

Background High incidence of late-onset sepsis (LOS) in preterm infants contributes to neonatal morbidity. Therapeutic outcomes of LOS have deteriorated as a result of increased antibiotic resistance problems, mainly from extended spectrum β-lactamase (ESBL) isolates. Controlling risk factors is important in reducing morbidity and mortality as well as providing guidance for antibiotic selection.

Objectives To determine the risk factors of LOS due to ESBL-producing bacteria in preterm infants.

Methods This is a retrospective study. The inclusion criteria was neonates diagnosed with late-onset neonatal sepsis by clinical signs and a positive blood culture. The blood culture result and characteristics patients as secondary data were extracted from medical records within the hospital facilities and the institutional database of the Neonatology Department of Universitas Brawijaya (January 2019 to March 2021). Statistical analysis was done to compare characteristics of the patients in the ESBL positive group to those in the ESBL negative group to assess the potential risk factors.

Results Among 124 preterm infants with LOS, 62 of them were ESBL-positive case subjects and the other 62 were non-ESBL-producing control subjects. Gram-negative bacteria were the most common pathogens identified, with 96% (n=59) of them being the ESBL-producing strain, predominated by Klebsiella pneumoniae (n=56). Factors significantly correlated with the occurrence of LOS-ESBL included prior history of invasive procedures (OR 3.13; 95%CI 1.45 to 6.73; P=0.00), central access insertion (OR 9.54; 95%CI 3.7 to 24.2; P=0.00), and parenteral nutrition (OR 6.03; 95%CI 2.77 to 13.16; P=0.00). Central access insertion had the strongest influence (Exp(B) 6.98; P= 0.00).

Conclusion Prior invasive procedures, central access insertion, and parenteral nutrition had significant correlations with the occurrence of LOS-ESBL in preterm infants. Central access insertion is a predictive factor for LOS-ESBL. **[Paediatr Indones. 2023;63:21-8; DOI: https://doi.org/10.14238/pi63.1sup.2023.21-8].**

Keywords: *late onset sepsis; ESBL; preterm; risk factor*

Neonatal sepsis is an important complication among neonates. Sepsis can lead to severe morbidities and mortality as well as increase the cost of medical care. The incidence of late-onset sepsis (LOS) is especially high among preterm infants and has become a serious concern in neonatology scope.[1,2]

Depending on the age at disease onset, neonatal sepsis can be categorized into early or late-onset sepsis (LOS). Early neonatal sepsis is mainly due to organisms acquired before and during delivery, whereas LOS is due to organisms acquired after delivery from nosocomial or community sources. In the past few decades, the mortality rate of LOS has remained at a high level (5-15%) in most neonatal care facilities.[3,4]

The therapeutic outcome of LOS has deteriorated, especially in developing countries, as a result of the widespread occurrence of antibiotic

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resistance, especially from pathogens producing extended-spectrum β-lactamase (ESBL), particularly in hospital environments.[5]

The ESBLs are enzymes produced by certain bacteria that can deactivate several antibiotics by hydrolyzing the amide bond in the β-lactam ring. The spectrum of enzyme activity is extended because of mutations in the gene encoding ESBLs.[6,7] The incidence of infections due to ESBL-producing organisms has increased in both children and adults.[7] This problem has a negative impact on patient outcomes, resulting in prolonged hospital stays, higher hospitalization costs, and increased mortality rates.[5]

Early recognition of ESBL colonization is important because it has been associated with subsequent invasive infections. Controlling risk factors can be an important action in the effort to reduce morbidity and mortality and can provide guidance for antibiotic selection.[7] However, few studies have described their clinical epidemiology in pediatric populations, especially neonates, and to the best of our knowledge, no published studies to date have focused on preterm infants.[8]

We aimed to determine the risk factors for LOS due to ESBL-producing bacteria in preterm infants.

Methods

This study was conducted in the Neonatology Unit of Saiful Anwar General Hospital, Malang, East Java, Indonesia. We used an analytical observational study design with a retrospective approach. Medical record data from January 2019 to March 2021 from within the hospital facilities and institution database of the Neonatology Department, Medical Faculty, Universitas Brawijaya, were extracted.

The inclusion criteria was neonates diagnosed with late-onset neonatal sepsis by clinical signs and a positive culture of a single potential pathogen from blood. Late-onset sepsis was defined as sepsis that occurred from 72 hours to day 28 of life. Management of neonatal illness and sepsis was per existing unit protocol. Blood cultures were done by the internal Microbiology Department under aseptic precautions using standard protocols for blood culture collection to isolate and identify the organism, evaluate antibiotic susceptibility patterns, and detect ESBL-producing organisms.

Patients showing positive for ESBL-producing bacteria in blood culture result were assigned to the case group, whereas those without ESBL-producing bacteria in blood culture result were assigned to the control group. Baseline characteristics of case and control subjects including gender, birth weight, gestational age, delivery method, length of stay, respiratory support, outcomes, surgical problem and intervention, NICU admission, invasive procedures, central acces insertion, and parenteral nutrition. Subject's characteristics were compared using Chi-square test. Exposure probability was analyzed using a 2x2 contingency table, and adjusted odds ratios (OR) with 95% confidence intervals (CI) were reported from this model. A stepwise regression test was performed to examine multivariate relationships between the covariates and each pair of groups. Results with P values ≤ 0.05 were considered to be statistically significant. Analyses were performed using the *SPSS statistics 26 for Windows* software. The study protocol was approved by the Ethics Committee of the institution.

Results

During the study period, a total of 2,347 infants were admitted to the hospital, of whom 248 (21%) had positive blood culture results. One hundred and ninety three (77.8%) positive blood culture were collected from preterm infants, in which 142 (73.5%) had LOS. Of these, 124 patients met the inclusion criteria, with 62 cases of infections caused by ESBL-producing isolates. The 62 ESBL-positive case subjects were compared to 62 patients with non-ESBL-producing infection as the control subjects.

The demographic information included mean gestational age, gender, birth weight, mode of delivery, and age of onset. Information related to medical exposure included the length of stay, respiratory support, surgical problem and intervention, NICU admission, antibiotics used, invasive procedures, central access insertion, and parenteral nutrition administration. The demographic characteristics of subjects are shown in **Table 1**.

More than half of the neonates in each group were male (65% of cases and 56% of controls).

Table 1. Demographic information of preterm neonates infected by ESBL- and non-ESBL-producing pathogens

Characteristics	ESBL (case) (n=62)	Non-ESBL (control) (n=62)
Gender, n(%)		
Male	40 (65)	35 (56)
Female	22 (35)	27 (44)
Birth weight, n(%)		
< 1,500 g	14 (23)	14 (23)
1,500-2,500 g	48 (77)	48 (77)
Mean (SD), g	1,929 (448)	1,962 (42)
Gestational age, n(%)		
Extremely preterm (< 28 weeks)	2 (3)	3 (5)
Very preterm (28-32 weeks)	16 (26)	17 (27)
Moderate-to-late preterm (32-37 weeks)	44 (71)	42 (67)
Mean (SD), weeks	32 (2.5)	32 (2.5)
Delivery method, n(%)		
Caesarean section	39 (63)	40 (65)
Vaginal delivery	23 (37)	22 (35)
Mean onset of sepsis (SD), days	11.7 (6)	12 (7)
Length of stay, n(%)		
≤ 7 days	20 (32)	18 (29)
> 7 days	42 (68)	44 (70)
Mean (SD), days	6.6 (5.1)	6.6 (6.9)
Outcomes, n(%)		
Survived	18 (29)	26 (42)
Died	44 (71)	36 (58)
Respiratory support, (%)		
Ventilator	32 (52)	22 (35)
CPAP	24 (39)	31 (49)
Nasal cannula	5 (8)	7 (11)
No support	1 (2)	2 (3)
Surgical problem, n(%)	30 (48)	21 (34)
Surgical intervention, n(%)	23 (37)	17 (27)
NICU admission, n(%)	30 (48)	16 (26)
Antibiotic history	62 (100)	62 (100)
Antibiotic usage, n(%)		
First line	62 (100)	62 (100)
Others	0	0
Antibiotic duration, n(%)		
≤7 days	31 (50)	23 (37)
> 7 days	31 (50)	39 (63)
Mean (SD), days	7.8 (2.9)	8.5 (2.6)
Invasive procedure, n(%)	47 (76)	31 (50)
Intubation/ETT	27 (44)	17 (27)
Transfusion	31 (50)	14 (23)
Surfactant	5 (8)	9 (15)
Central access type, n(%)	55 (89)	28 (45)
Umbilical catheter	7 (11)	7 (11)
CVC	48 (77)	21 (34)
Parenteral nutrition, n(%)	46 (74)	19 (31)

ETT=endotracheal tube; CVC=central venous catheter

Mean birth weight did not differ much between the two groups [1,929 (SD 448) *vs.* 1,962 (SD 442) g, respectively], with the largest proportion in the 1,500-2,500 g range (77%); the rest of the infants weighed < 1,500 g. Both groups had mean gestational age of about 32 (SD 2.5) weeks. The majority of subjects

were moderate-to-late preterm (32-37 weeks) infants, and extremely preterm babies with <28 weeks gestation comprised 3% of the case group and 5% of the control group. In both groups, the most common delivery method performed was caesarean section [39 (63%) *vs.* 40 (65%), respectively].

The onset age of sepsis was also similar between the two groups [11.7 (SD 6) days *vs.* 12 (SD 7) days, respectively]. All neonates had a prior history of antibiotic administration at admission, with ampicillin-gentamycin combination as a first-line empirical therapy. Mean antibiotic duration was 7.8 (SD 2.9) days in the case group and 8.5 (SD 2.6) days in the control group.

An invasive procedure was performed on 47 (76%) of neonates in the case group and 31 (50%) in the control group. Procedures included endotracheal intubation, transfusion, and surfactant administration. The proportion of neonates who underwent central access insertion was larger in the case group (55; 89%) than in the control group (28; 45%). The most frequently performed central access type was central venous catheters (CVC) (48.8% *vs.* 34%, respectively) rather than an umbilical catheter. Parenteral nutrition was given to 48 (74%) case subjects and 19 (31%) controls. Less than half of both groups had been admitted to the NICU (48% and 26%, respectively). However, almost all infants who had been admitted to NICU required respiratory support, including a ventilator or continuous positive airway pressure (CPAP).

The prevalence of ESBL infection (n=68) over the whole of positive blood culture (n=248) was 27%. Gram-negative bacteria were the most common pathogens found (84/124; 68%). Isolates were predominantly *Klebsiella pneumoniae* (56/124; 45%), with 54/56 (96.5%) ESBL-producing strains followed by Staphylococcal sp. (39/124, 31% of isolates). The characteristics of positive isolates are shown in **Table 2**.

The mortality rate was 71% in the ESBL isolate group and 58% in the non-ESBL isolate group. Possible risk factors for infection with ESBL-producing organisms are listed in **Table 3**. There were no significant demographic differences between the case group and control. Caesarean section as the mode of delivery, prolonged hospital stay, history of NICU admission, and antibiotic exposure were predisposing conditions to ESBL, but they were not statistically significant. The significant risk factors for preterm for having ESBL-LOS were the presence of invasive procedure (OR 3.13; 95%CI 1.45 to 6.73; P=0.00), central access insertion (OR 9.54; 95%CI 3.7 to 24.2; P=0.00), and parenteral nutrition administration (OR 6.03; 95%CI 2.77 to 13.16; P=0.00).

Table 2. Characteristics of bacterial isolates (N=124)

Isolates	n (%)
Klebsiella pneumoniae	56 (45)
ESBL (XDR=3)	54
Staphylococcal sp.	39 (31.5)
Coagulase-negative staphylococcus	14
Coagulase-negative Staphylococcus resistant strain	9
Staphylococcus haemolyticus	9
Staphylococcus hominis	3
Staphylococcus aureus	1
Staphylococcus aureus MRSA	3
Acinetobacter baumanii	6 (4.8)
XDR(ESBL)	3
Pseudomonas aureginosa	5 (4)
XDR (ESBL)	2
Escherichia coli ESBL	3 (2)
Enterobacter cloacae	3 (2)
Serratia marcescens	2 (1.8)
Enterococcus faecalis	2 (1.8)
Acinetobacter lwoffii	1 (1)
Burkholderia cepacia	1 (1)
Stenotrophomonas maltophilia	1 (1)
Turicella otitidis	1 (1)
Pasteurella pneumotropica	1 (1)
Bacillus cereus	1 (1)
Proteus hauseni	1 (1)
Enterococcus gallinarum	1 (1)
Total	124 (100)

When differentiated specifically by type of procedure, blood component transfusion was a significant factor with an OR of 3.42 (95%CI 1.57 to 7.45; P=0.02), rather than intubation (OR=2.04; 95%CI 0.96 to 4.32; P=0.06) and surfactant administration (OR=0.517; 95%CI 0.16 to 1.64; P=0.26). Central venous catheter (CVC) was a significant factor in the central access variable (OR 6.7; 95%CI 3 to 14; P=0.00) rather than umbilical catheter (OR=1; 95%CI 0.3 to 3; P=1.00).

In multivariate analysis, factors that retained significance through the regression model were central

Table 3. Univariate analyses of risk factors for subjects with ESBL and non-ESBL isolates

Variables	ESBL (n=62)	Non-ESBL (n=62)	OR (95%CI)	P value
Birth weight, n				
< 1,500 g	14	14		
1,500-2,500 g	48	48	0.823 (0.34 to 1.95)	0.66
Mean (SD), g	1,929 (448)	1,962 (442)		0.68
Mean gestational age (SD), weeks	32 (2.5)	32 (2.5)		0.19
Length of stay				
≤ 7 days	20	18	1.24 (0.588 to 2.63)	0.57
> 7 days	42	44		
Mean (SD), days	6.6 (5.1)	6.6 (6.9)		0.96
Antibiiotic duration				
≤ 7 days	31	23		
> 7 days	31	39	0.59 (0.3 to 1.2)	0.15
Mean (SD), days	7.8 (2.9)	8.5 (2.6)		0.12
NICU admission	30	16	0.871 (0.42 to 1.80)	0.71
Ventilator support	32	22	1.9 (0.9 to 3.9)	0.07
Surgical case	30	21	0.55 (0.265 to 1.127)	0.10
Surgical intervention	23	17	0.641 (0.30 to 1.369)	0.25
Invasive procedure	47	31	3.13 (1.45 to 6.73)	0.00
Intubation/ETT	27	17	2.04 (0.96 to 4.32)	0.06
Transfusion	31	14	3.42 (1.57 to 7.45)	0.02
Surfactant	5	9	0.517 (0.16 to 1.64)	0.26
Central access	55	28	9.54 (3.7 to 24.2)	0.00
Umbilical catheter	7	7	1 (0.3 to 3)	1.00
CVC	48	21	6.7 (3 to 14)	0.00
Parenteral nutrition (PN)	46	19	6.03 (2.77 to 13.16)	0.00
PN through CVC	41	15	2.187 (0.52 to 9.25)	0.29

access insertion [Exp(B) 6.98; 95%CI 3.12 to 15.59; P=0.000] and parenteral nutrition [Exp(B) 4.98; 95%CI 2.12 to 11.45; P=0.000] (**Table 4**).

The remarkable finding from this study was that the main risk factors for LOS caused by ESBL infection in preterm infants were central access insertion and parenteral nutrition.

Table 4. Multivariate analysis of all variables observed

Variables	Exp(B)	95% CI	P value
Parenteral nutrition	4.98	2.12 to 11.45	0.000
Central access	6.98	3.12 to 15.59	0.000

Discussion

The ESBL infections are increasing dramatically across the globe. Genes encoding ESBLs are often carried on mobile genetic elements, such as plasmids, which are capable of rapid spread and dissemination. The ESBL infections have also been found to have a negative impact on patient outcomes, such as increased hospital costs, length of stay, and mortality rates.[5,9]

The general prevalence of ESBL infection in this centre, means the number of ESBL pathogen over the whole of positive blood culture, reach 27%, higher compared to a previous study in a developed country (1.7%), but lower compared to another study in India (5.3%).[5,8]

A previous study in neonates, not based on gestational age, reported an incidence of ESBL-producing agents in LOS of 65%, and *Klebsiella*

pneumonia was the predominant isolate.[10] In our study, the prevalence of LOS specifically in preterm infants with positive blood cultures was 73.5% and 49.6% of the these prevalence showed ESBL-producing bacteria in the isolates. Similar to other studies, the blood culture results in the ESBL group were predominantly *Klebsiella pneumonia* ESBL (87%).[8,10,11]

Preterm and low birth weight neonates are more susceptible to ESBL-producing organism infections. This observation is mainly attributed to their immature immune systems. They are also more likely to undergo many interventional procedures.[8] A previous study reported that ESBL colonization was significantly higher in neonates with prematurity, prior antibiotic history, hospital stay, parenteral nutrition, and who underwent other invasive procedures, such as caesarean delivery, respiratory support including ventilator or CPAP, endotracheal intubation, central venous catheter insertion, umbilical catheter, surgical intervention, and blood component transfusions. These procedures may increase the risk of internal colonization (including of the respiratory tract, digestive tract, and blood) with ESBL-producing bacteria.[5,7,11] A previous study reported on risk factors of LOS in preterm infants, including length of hospitalization, indwelling devices such as central venous catheters, urinary catheters, tracheostomy, and endotracheal tubes, total parenteral nutrition duration, antibiotic therapy, and surgical procedures.[12]

The number of subjects in our analysis was comparable to that in other pediatric studies, and we were able to observe many contributing factors from previous studies[5,10] but specifically in preterm infants. The significant risk factors for LOS-ESBL in our preterm subjects were the history of invasive procedures, particularly central access, and parenteral nutrition administration. Invasive procedures assessed in our study included any of endotracheal tube insertion, surfactant administration, and transfusion procedures.

A study showed that central access was not a significant factor.[13] However, other studies about ESBL colonization noted that central access, especially CVC, had a significant role in ESBL infection.[11,12] Our study suggested that central access was associated with increased LOS-ESBL incidence, with central venous catheter (CVC) insertion associated with a higher LOS-ESBL risk compared to an umbilical catheter.

Similar to findings by Sharma *et al.*[10] we noted that parenteral nutrition was a risk factor for ESBL-producing organisms in neonates. Empirical use of antibiotics, such as third-generation cephalosporins or ampicillin-gentamicin combination therapy, is a common treatment for infections, which may bring significant selective pressure on resistant strains and lead to infection or colonization with ESBL-producing pathogens.[7] Prior antibiotic use was also a significant risk factor for ESBL isolates, and specified as one of the major risk factors in other studies.8,14 Unfortunately, in our study, antibiotic exposure could not be interpreted because all subjects received the same first-line antibiotic therapy.

Interestingly, LOS-ESBL incidence was not significantly associated with length of stay, NICU admission, surgical intervention, operative procedure, or mechanical ventilation, as found in previous studies. This difference may have been due to general characteristics of our subjects, as previous studies were not based on gestational age. Our study also recorded several other colonizations that was not specific to ESBL isolates.[8,10,11,15,16] In our study, LOS-ESBL was not associated with gestational age or specific type of prematurity. Neonates, particularly extremely low birth weight, were more prone to these infections.[8]

The remarkable findings from our study were that central access insertion and parenteral nutrition were the main risk factors for LOS caused by ESBL infection in preterm infants. Central access was a predictor or factor that had the strongest influence on the occurrence of LOS-ESBL in preterm infants (OR=9.54; CI 95% 3.7 to 24.2).

Our study had several limitations. As a single-center study, our findings must be repeated in a larger and more diverse setting. Also, we used a retrospective study design with a relatively small sample size, which might have allowed for selection bias. Additionally, although we completed a thorough review of inpatient records, data may have been missing. In addition, we may not have captured the medical staff quality, including hygiene and insight about nosocomial infection and antibiotic resistance that is related to resistant pathogen infection in other general studies.[17,18]

In conclusion, invasive procedures, central access insertion, and the provision of parenteral nutrition have a significant correlation with the

occurrence of LOS-ESBL. The presence of central access is a predictor or factor with the greatest influence on the occurrence of LOS-ESBL in preterm infants. Strict infection control interventions and antimicrobial stewardship should be maintained in handling neonates, especially preterm and low birth weight neonates, to control risk factors and decrease LOS-ESBL incidence. Longitudinal surveillance of the microbial flora and their antibiotic sensitivity patterns should be done periodically in all hospitals to identify the existing flora and establish appropriate management of infection by these organisms.

Conflict of interest

None declared.

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