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Original Article

116 cases of neonatal early-onset or late-onset sepsis: A single center retrospective analysis on pathogenic bacteria species distribution and antimicrobial susceptibility

Zhiling Li[1,3], Zhijun Xiao[1], Zhiping Li[2], Qiao Zhong[3], Ye Zhang[1], Feng Xu[1]

[1]Department of Pharmacy, Fengxian Hospital, Southern Medical University, Shanghai 201400, China; [2]Department of Pharmacy, Children's Hospital, Fudan University, Shanghai 201102, China; [3]Department of Pharmacy, Shenzhen Maternal & Child Care Hospital, Southern Medical University, Shenzhen 518028, China

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Abstract: *Purpose:* The aim of this study was to explore the risk factors, clinical symptoms, hematological parameters, causative pathogen and antibiotic susceptibility of neonatal sepsis in a Chinese NICU. *Methods:* A retrospective survey was conducted on 116 cases of neonatal sepsis in NICU at the Maternal and Child Care Hospital in Shenzhen, China from January 2009 to December 2012. Patients were divided into early-onset sepsis (EOS) and late-onset sepsis groups according to their positive blood culture occurrence time (in the first 7 days of life or later). *Results:* 116 cases of neonatal sepsis were divided into early-onset sepsis (EOS) group and late-onset sepsis (LOS) group. There was significant difference for risk factors like peripherally insertion central catheter (PICC) between two groups. The clinical symptoms or laboratory results such as chilly periphery, fever, jaundice, platelet and hemoglobin also had between-group differences. The most common responsible pathogenic bacteria species present in EOS group was Coagulase-negative Staphylococcus (CoNS). Among those CoNS Staphylococcus epidermidis provided 24.24%, and Staphylococcus haemolyticus contributed 13.63%. Both were sensitive to vancomycin, teicoplanin and linezolid. The most common responsible pathogenic bacteria species in LOS group was Staphylococcus epidermidis (16%). Antimicrobial susceptibility in EOS group is higher than in LOS group. *Conclusion:* PICC is a bigger risk factor for neonatal late-onset sepsis. Staphylococcus epidermidis was the leading pathogen present in neonatal sepsis in a tertiary maternal & child care hospital in southern China. Vancomycin, teicoplanin and linezolid may be the best choice to management of neonatal sepsis.

Keywords: Early-onset sepsis, late-onset sepsis, antimicrobial susceptibility, NICU, China

Introduction

Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life [1]. To date, neonatal sepsis remains a serious problem in neonatal intensive care unit (NICU), resulting in significant morbidity and mortality [2]. The World Health Organization (WHO) estimates that more than one million neonatal deaths around the world each year are caused by severe infections, and around one million deaths are due to neonatal sepsis or pneumonia alone [3]. Morbidity of neonatal sepsis differs significantly from country to country. Incidence of neonatal sepsis varies from 1 to 5 cases per 1000 live births in developed countries, but gets higher in developing countries which varies from 49 to 170 per 1000 [4]. Thus, early diagnosis and treatment of neonatal sepsis is especially vital in China.

Neonatal sepsis can be classified into two types based on the postnatal ages at onset: early-onset neonatal sepsis (EOS) occurs in the first seven days, whereas late-onset neonatal sepsis (LOS) occurs after the seventh day. EOS is caused by microorganisms from the maternal

Table 1. Risk factors of EOS and LOS

Risk factor	Number and percentage			*p* value
	EOS (N = 66)	LOS (N = 49)	Total (N =115)	
PICC	9 (13.64)	19 (38.78)	28 (24.35%)	0.002*
Trachea cannula	4 (6.06)	6 (12.24)	10 (8.70%)	0.321
Use of incubator	13 (19.70)	16 (32.65)	29 (25.22%)	0.114
Intravenous nutrition	13 (19.70)	16 (32.65)	29 (25.22%)	0.114

Abbreviation: PICC, peripherally insertion central catheter. *$p < 0.05$ means a significant difference between EOS and LOS groups.

Table 2. Clinical symptoms in EOS and LOS groups

Clinical symptoms	Number and percentage			*p* value
	EOS (N = 66)	LOS (N = 49)	Total (N = 115)	
Chilly periphery	7 (10.61%)	13 (26.53%)	20 (17.40%)	0.026*
Low Response	13 (19.70%)	17 (34.69%)	30 (26.09%)	0.070
Fever	11 (16.67%)	26 (53.06%)	37 (32.17%)	0.000*
Cyanosis	23 (34.85%)	14 (28.57%)	37 (32.17%)	0.476
Jaundice	9 (13.64%)	15 (30.61%)	24 (20.87%)	0.027*
Daily amount of milk	6 (9.09%)	5 (10.20%)	11 (9.57%)	1.000

*$p < 0.05$ means a significant difference between EOS and LOS groups.

genital tract before or at the time of birth, while LOS is due to organisms acquired after delivery and considered nosocomial community-acquired infections [5]. Since China has a vast area, the climate of northern and southern China differs quite, the prevalence and distribution of pathogens varies widely around the country. It is important to recognize the common pathogens and related drug sensitivities for individual hospital [2]. In additional, it is crucial to dynamically monitor the local epidemiology of neonatal sepsis to detect any changes in infection patterns and drug sensitivity.

Materials and methods

Study design and patient population

A retrospective study was conducted in NICU of Shenzhen Maternal & Child Care Hospital (SZMCH), Shenzhen, China. The study protocol was approved by the Hospital Clinical Research Ethics Committee of SZMCH. Neonates (0-28 days) with the clinical signs and symptoms of sepsis at the time of admission or who developed sepsis during hospital stay were included in this study.

Through database searches, the information including risk factors and clinical symptoms (such as trachea cannula, intravenous nutrition, low response), hematological parameters, pathogen features, major bacteria's resistant organism detection rate and antimicrobial resistance were reviewed from patients' medical record. Patient data was recorded on a standardized data collection form.

Blood cultures were obtained from infants with clinical signs suggestive of sepsis. All blood samples were collected prior to initiation of antimicrobial therapy. Neonatal sepsis was defined as the growth of single potentially pathogenic organism (bacterium or fungus) from blood in patients with clinical and laboratory findings consistent with infection [6]. Patients were divided into EOS (0-7 days) and LOS (8-28 days) groups. A few infants had more than one episode of sepsis. If the organism was cultured after 10 days of appropriate antimicrobial therapy or a different organism was cultured from a subsequent culture, this was considered an additional episode.

Susceptibility testing

The antimicrobial susceptibility for isolated pathogens was determined and met all the recommendations of the National Committee of Clinical Laboratory Standards breakpoint values. Antimicrobial susceptibility testing of isolated pathogens was done with ATB susceptibility systems (BioMerieux La Balmes-les Grottes, France) by using the Kirby Bauer disk diffusion method.

Data analysis

Data was entered in Excel 2010 database (Microsoft, USA) and analyzed using SAS software version 9.1 (SAS, USA). The differences in distribution of categorical factors were assessed using Mantel-Haenzel chi-square test or Fisher's Exact Test as appropriate. Proportions were compared by χ^2 test. A *p*-value ≤ 0.05 was considered statistically significant.

Table 3. Hematological parameters in EOS and LOS groups

Hematological parameters	$\bar{\chi} \pm s$		*p* value
	EOS (N = 66)	LOS (N = 49)	
White blood cell counts (10E/L)	13.38 ± 8.36	12.04 ± 6.49	0.339
Lymphocyte counts (10E/L)	4.51 ± 3.31	4.49 ± 2.34	0.976
Neutrophil cell counts (10E/L)	6.99 ± 5.90	5.69 ± 5.01	0.224
Platelet counts (10E/L)	212.40 ± 86.36	278.37 ± 144.90	0.006*
Hemoglobin (g/L)	154.42 ± 29.82	126.52 ± 31.01	0.000*
C-reactive protein (mg/L)	30.58 ± 37.06	34.12 ± 40.44	0.728

*$p < 0.05$ means a significant difference between EOS and LOS groups.

Table 4. Number and percentage of pathogens isolated from patients with neonatal sepsis

Pathogens	Number and percentage	
	EOS	LOS
Gram-positive bacteria	55 (83.33%)	35 (70.00%)
Coagulase-positive Staphylococcus (CoPS)	1 (1.52%)	2 (4.00%)
Staphylococcus aureus	1 (1.52%)	2 (4.00%)
Coagulase-negative Staphylococcus (CoNS)	44 (66.67%)	27 (54.00%)
Staphylococcus epidermidis	16 (24.24%)	8 (16.00%)
Staphylococcus haemolyticus	9 (13.63%)	5 (10.00%)
Staphylococcus capitis	7 (10.61%)	6 (12.00%)
Staphylococcus hominis	6 (9.09%)	3 (6.00%)
Staphylococcus warneri	0 (0.00%)	5 (10.00%)
Staphylococcus caprae	3 (4.54%)	0 (0%)
Staphylococcus saprophyticus	2 (3.03%)	0 (0%)
Staphylococcus coliform	1 (1.52%)	0 (0%)
Enterococcus faecalis	7 (10.61)	3 (6.00%)
Group B streptococcus (GBS)	3 (4.54)	3 (6.00%)
Gram-negative bacteria	11 (16.67%)	15 (30.00%)
Klebsiella pneumoniae	7 (10.61%)	6 (12.00%)
Escherichia coli (*E. coli*)	4 (6.06%)	7 (14.00%)
Acinetobacter baumannii	0 (0%)	2 (4.00%)
Total	66	50

Abbreviation: CoPS, Coagulase-positive Staphylococcus; CoNS, Coagulase-negative Staphylococcus; GBS, Group B streptococcus; *E. coli*, Escherichia coli.

Results

Incidence

Between January 1, 2009 and December 31, 2012, there were 5076 neonates admitted to the NICU. Of these, 115 neonates with 116 episodes of sepsis were included in this study. The incidence of sepsis was 2.27% among all NICU infants. There were 66 episodes in 66 infants of EOS and 50 episodes in 49 infants of LOS. 114 (99%) infants had a single episode of sepsis. 1 (0.86%) infants had two episodes of sepsis.

Risk factors of neonatal sepsis

The risk factors of neonatal sepsis were showed in **Table 1**. The percentages of use of incubator, intravenous nutrition and peripherally insertion central catheter (PICC) in all patients were 25.22%, 25.22% and 24.35% respectively. There were statistically significant difference in PICC between the EOS and LOS group ($p < 0.05$).

Clinical symptoms of neonatal sepsis

Cyanosis (34.85%) and low response (19.70%) were the most common clinical presentations in EOS group, while fever and low response were the major clinical symptoms in LOS group. There were statistically significant difference in chilly periphery, fever and jaundice between the two groups ($P < 0.05$) (**Table 2**).

Hematological parameters

The results of hematological parameters were presented in **Table 3**. White blood cell (WBC) counts, differential counts and C-reactive protein (CRP) drawn on the first day of sepsis in EOS group and LOS group were available for 66 and 49 episodes, respectively. There were no statistically significant difference between the counts of the WBC, lymphocytes, neutrophils, and the CRP value between two groups. Platelet (PLT) in the LOS group was significantly higher than that in the EOS group ($p < 0.005$), while the Hemoglobin (HGB) in the LOS group was lower than that in the EOS group ($p < 0.05$).

Distribution of pathogens

Number and percentage of pathogens isolated from patients with neonatal sepsis were shown

Table 5. Drug resistance rate of pathogens isolated in EOS and LOS group

Pathogenic bacteria	EOS		LOS		*p*-value
	Pathogens No.	No. (%) of resistant	Pathogens No.	No. (%) of resistant	
CoNS	44	40 (90.9)	27	25 (92.6)	> 0.05
Staphylococcus aureus	1	1 (100)	2	2 (100)	> 0.05
Klebsiella pneumoniae	7	6 (85.7)	6	6 (100)	> 0.05
E. coli	4	3 (75)	7	6 (85.7)	> 0.05

Abbreviation: CoNS, Coagulase-negative Staphylococcus; *E. coli*, Escherichia coli.

Table 6. Pathogens susceptibility to antimicrobials between EOS group and LOS group

Antibacterials	EOS		LOS		*p*-value
	Pathogens No.	No. (%) of resistant	Pathogens No.	No. (%) of resistant	
Penicillin	49	46 (93.9)	21	21 (100)	> 0.05
Oxacillin	48	45 (93.8)	21	19 (90.5)	> 0.05
Cefoxitin	35	33 (94.3)	14	14 (100)	> 0.05
Amoxicillin/clavulanic acid	42	37 (88.1)	16	13 (81.3)	> 0.05
Tetracycline	42	3 (7.1)	16	5 (31.3)	< 0.05*
Erythromycin	34	3 (8.8)	18	14 (77.8)	< 0.001*
Gentamicin	43	29 (67.4)	18	10 (55.6)	> 0.05
Amikacin	35	5 (14.3)	16	3 (18.8)	> 0.05
Ciprofloxacin	45	27 (60)	21	11 (52.4)	> 0.05
Ampicillin	43	41 (95.3)	17	16 (94.1)	> 0.05
Vancomycin	41	3 (7.3)	20	2 (10.0)	> 0.05
Teicoplanin	43	10 (23.3)	17	0 (0)	< 0.05*
Linezolid	38	0 (0)	19	0 (0)	

*$p < 0.05$ means a significant difference between EOS and LOS groups.

in **Table 4**. Gram-positive bacteria accounted for 83.33% of early-onset infections and 70% of late-onset infections. Coagulase-negative Staphylococcus (CoNS) is the major Gram-positive bacteria both in EOS (66.67%) and LOS (54.4%) groups. The most common pathogens were staphylococcus epidermidis (24.24%) and staphylococcus haemolyticus (13.63%) in EOS group, while the major causative microorganisms were Staphylococcus epidermidis (16%) and Escherichia coli (*E. coli*) (14%) in LOS group.

Antimicrobial susceptibility

Antimicrobial susceptibility of pathogens isolated in EOS and LOS group was presented in **Tables 5** and **6**. In EOS group, the resistance rate of staphylococcus aureus, CoNS klebsiella pneumonia and *E. coli* is 100%, 90.9%, 85.7% and 75% respectively. In LOS group, the resistance rate of staphylococcus aureus and klebsiella pneumonia, CoNS and *E. coli* is 100%, 100%, 92.6%, and 85.7%, respectively. There was no statistically significant difference between these two groups in their resistance rate.

Most of the bacteria were resistant to penicillin, oxacillin, cefoxitin and ampicillin. All bacteria were susceptible to linezolid. The resistance rates of tetracycline, erythromycin in the LOS group was higher than that in the EOS group, while the resistance rates of teicoplanin in the LOS group was lower than that in the EOS group.

Discussion

The diagnosis of neonatal sepsis is difficult because clinical signs, particularly early in the course of disease, are hard to distinguish from other causes of neonatal disease [7]. Blood culture has been considered as gold standard for detecting bacterial sepsis [8]. However, blood culture is time-consuming and the distribution of pathogens association with neonatal sepsis is wide. Thus, for early diagnosis and treatment of the disease, it is meaningful to

continue sum up and analyzes the clinical signs, pathogenic bacteria and antimicrobial resistance of neonatal sepsis.

The incidence rate of sepsis was 2.27% in this study, which is compatible with other reports [9, 10]. This study shows that use of incubator, intravenous nutrition and PICC are risk factor of neonatal sepsis and PICC is a higher risk factor of EOS. Some published studies have documented that risk factors for EOS include prematurity and associated immunologic immaturity, maternal GBS colonization, rupture of membranes greater than 18 hours, and maternal intra-amniotic infection [11-13]. A recent study indicated that 36% of 9,575 extremely low-gestational-age infants (22 to 28 weeks) developed LOS; suggesting extreme prematurity is a risk factor of LOS [14].

Early initiation of antimicrobial therapy is frequently delayed because the first clinical signs of sepsis are non-specific [15]. In our study, we found that chilly periphery, fever, jaundice and cyanosis account for a large proportion of clinical manifestation in infants with sepsis. Chilly periphery, fever and jaundice may be signs to help differentiate EOS and LOS.

In clinical work, various serologic markers such as CRP, WBC counts, lymphocytes, neutrophils are often used to support the diagnosis of sepsis [16]. We found that there is no statistically significant difference between the counts of the WBC, lymphocytes, neutrophils, and the CRP value of the EOS and LOS groups, which were consistent with previous study [17]. However, PLT in the LOS group was significantly higher than that in the EOS group, while HGB in the LOS group was lower than that in the EOS group.

With the extensive use of antimicrobials, the composition of pathogens causing neonatal sepsis has also changed dramatically over the last century [18]. In the 1970 s, GBS infections were considered as the leading cause of EOS and meningitis [19]. In the past decade, some studies revealed that *E. coli* have become a growing problem in EOS [20-22]. However, in our study, *E. coli* is a major pathogen in LOS group. Gram-positive microorganisms were found to be the most common causative pathogen in both EOS and LOS groups. And CoNS is the major pathogen. The common isolates were Staphylococcus epidermidis, followed by staphylococcus haemolyticus, which were consistent with studies conducted in China and other developing countries [23-26].

The resistance rates of tetracycline, erythromycin in the LOS group was significantly higher than that in the EOS group, while the resistance rates of teicoplanin in the LOS group was lower than that in the EOS group. Amikacin and tetracycline are lower resistance in EOS, but they generally not be considered due to the physiological characteristics of the neonates. The widespread use of vancomycin in NICUs may result in vancomycin-resistant strains of pathogens such as enterococci. A multicenter survey of neonatologists' practices in the treatment of neonates with suspected late-onset sepsis found that, in 83% of centers surveyed, at least 75% of survey respondents had similar practices with regard to prescribing a vancomycin-containing regimen for empiric therapy [27]. Substitution of oxacillin for vancomycin as the empiric antimicrobial for suspected gram-positive sepsis had no effect on the frequency of fulminate sepsis for CoNS [28].

In short, from the comparative study of the NICU sepsis cases of EOS and LOS, some characteristics can be found as following: (1) EOS and LOS have their own characteristics in risk factor and clinical symptoms. (2) In EOS, the most common pathogens responsible included Staphylococcus epidermidis and Staphylococcus haemolyticus. The most common causative micro organisms in LOS were Staphylococcus epidermidis and *E. coli*; (3) The LOS group has a higher resistant rate to common antibacterial than EOS group. CoNS is sensitive to Vancomycin, Teicoplanin and Linezolid; Klebsiella pneumonia is relatively sensitive to imipenem, Meropenem, Piperacillin/Tazobactam. Limitations of this study are its restriction to a single medical center and retrospective review method.

Conclusions

In conclusion, Staphylococcus epidermidis was found to be the leading pathogen in early-onset sepsis. The most common causative microorganisms of late-onset sepsis were Staphylococcus epidermidis and *E. coli*. Better medical decision, especially for appropriate choices for early detection and initial antimicrobial therapy,

can be made by understanding the different clinical features and pathogen of EOS and LOS.

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Address correspondence to: Dr. Feng Xu, Department of Pharmacy, Fengxian Hospital, Southern Medical University, Shanghai 201400, China. Tel: +86-21-57422032; E-mail: andrewfxu1998@gmail.com

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