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Management of early-onset sepsis in a teaching hospital: A descriptive retrospective study

Sana H. Mohamed[1], Rasha R. Binni[2], Bashir A. Yousef[2,3]✉

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, University of Khartoum, Al-Qasr Ave, Khartoum 11111, Sudan

[2]Department of Pharmacology, Faculty of Pharmacy, Sudan International University, Ebid-Khatim Street, Khartoum 11111, Sudan

[3]Department of Pharmacology, Faculty of Pharmacy, University of Khartoum, Al-Qasr Ave, Khartoum 11111, Sudan

ABSTRACT

Objective: To evaluate the management of early-onset sepsis at Saad Abul-Ella Teaching Hospital, Sudan.

Methods: A descriptive retrospective hospital-based study was carried out at the Nursery Department of Saad Abul-Ella Teaching Hospital. All medical records of neonates with suspected or confirmed sepsis during the year 2017 were reviewed to evaluate the management of antibiotics for sepsis using a data collection form.

Results: Out of the 205 cases, 82 neonates (40%) were diagnosed as early-onset sepsis, among which the majority was male (68%). All neonates were given cefotaxime plus vancomycin as empirical therapy which was changed to other antibiotics in 23% of the cases. The common risk factors associated with early-onset sepsis wereprolonged rupture of membrane (41.8%), preterm delivery (26.3%) and low birth weight (15.1%). Blood cultures were performed in 168 cases, and 19% had bacterial growth of *Staphylococcus aureus* which is the most common isolated pathogen.

Conclusions: Cefotaxime plus vancomycin are the main empirical antibiotic for sepsis, and *Staphylococcus aureus* is the most common pathogen associated with early-onset sepsis.

KEYWORDS: Umbelliferone; Type 2 diabetes mellitus; Oxidative stress; Inflammation; Glycation

1. Introduction

According to the proceedings of the International Pediatric Consensus Conference (2005), neonatal sepsis is defined as "a systemic inflammatory response syndrome in the presence of or as a result of suspected or proven infection". In the first four weeks of onset, neonatal sepsis can cause severe complications (acute lung injury, cardiac dysfunction, hemorrhage, hepatic failure, renal failure, multiple organ dysfunction syndromes, death, *etc.*) in nursery intensive care unit (NICU)[1]. The incidence of clinically diagnosed neonatal sepsis in developing countries is 49 to 170 per 1 000 live births, and the culture proved sepsis is 16 per 1 000 live births, and neonatal meningitis is 0.8 to 6.1 per 1 000 live births[2-4]. The reason for the high rates of infection in developing countries could be lack of formal health care for the mother and baby in the first few days post-delivery, as a significant proportion of births occurred at home. In addition, mothers do not receive adequate antenatal care. Other factors include the lack of skilled birth attendants or the presence of unskilled ones who cut the umbilical cord by non-sterile methods and cannot discover the warning signs of infection on both the mother and baby[5]. Convulsions, lethargy, inability to feed, cyanosis, the premature rupture of membranes (PROM), and meconium stained liquor were efficient predictors of both early and late-onset neonatal sepsis with positive blood culture[6].

Determination of the bacteriological profile and the pathogenic organisms allows the selection of properly targeted antibiotics to treat sepsis[7]. In developing countries, several pathogenic bacteria were associated with early-onset sepsis (EOS), such as *Staphylococcus aureus* (*S. aureus*), Group B *streptococcus*, *Escherichia coli*, *Klebsiella spp*, and *Salmonella spp.*[5,8,9]. In order

✉To whom correspondence may be addressed. E-mail: bashiralsiddiq@gmail.com

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to prevent the rapid deterioration of sepsis, an empirical broad-spectrum antibiotic should be initiated to all young infants with suspected bacterial infections[8]. If the results of blood culture are negative, and the infant presents no further symptom after 48 h, antibiotic therapy can be ceased[10,11]. But this kind of practice exposes the infant to a large number of unnecessary antibiotics, as positive blood cultures are only shown in 5%-10% of suspected sepsis cases[12,13].

The World Health Organization recommends a two-day administration of prophylactic ampicillin and gentamicin for neonates with high-risk factors, and gentamicin plus benzylpenicillin or ampicillin for 7-10 d for the confirmed cases. For higher risk of *staphylococcus* infection, it recommends intravenous cloxacillin plus gentamicin for at least 7 to 10 d, whereas intramuscular gentamicin plus oral amoxicillin are recommended for the young infant for whom the hospital is not accessible[14]. Moreover, Sudanese guidelines recommend the use of ampicillin plus gentamicin or amikacin for septicemia for 7-14 d[15].

The common pathogens of neonatal sepsis in developing countries differ from those in developed countries[16]. Zea-vera *et al.* stated that there are no sufficient studies to determine the epidemiology of neonatal sepsis in developing countries, including Sudan[5]. Additionally, the irrational use of antibiotics associated with the growth and spread of resistant pathogens in the NICU makes the situation worse. Thus, this study was conducted to evaluate the risk factors and management of early neonatal sepsis at Saad Abul-Ella Teaching Hospital, which may help in future planning to prevent EOS, reduce antibiotics misuse, and lower neonatal mortality.

2. Materials and methods

2.1. Study design

A descriptive retrospective hospital-based study was conducted at Saad Abul-Ella Teaching Hospital, Khartoum, Sudan from January to December 2017.

Medical records of all neonates admitted to the hospital with suspected or confirmed sepsis during the study period were included in this study. The eligibility criterion was the neonates (aged 0-72 h) with suspected or confirmed neonatal sepsis. Neonates aged above 72 h and those with diseases other than neonatal sepsis were excluded. Accordingly, a total number of 205 records were recruited.

The medical records were reviewed, and data were extracted using a well-designed form, which contains patient demographic data (age, weight, and gender), clinical characteristics (term, hospitalization period, and risk factors), selection of antibiotics, blood culture, C-reactive protein (CRP), and the treatment outcomes.

2.2. Statistical analysis

SPSS version 23 was used to analyze the data. The data were expressed as frequency and percentages. *Chi*-square test was applied to analyze the associations between categorical variables. The significance level of the test was set at α=0.05.

2.3. Ethics approval

The ethical clearance (FPEC-13-2018) was obtained from the Ethical Committee of the Faculty of Pharmacy, University of Khartoum. An additional official agreement was obtained from Saad Abul-Ella Teaching Hospital to check the medical record. All medical records were coded with ensuring confidentiality throughout the study.

3. Results

In this study, 205 records of the neonates with suspected neonatal sepsis who admitted to Saad Abul-Ella Teaching Hospital during the year 2017 were enrolled. The incidence of neonatal sepsis among them was 40%. Table 1 shows the demographic characteristics of the participants. The majority (91.2%) of enrolled neonates were within the age of one day. A total of 127 (62.0%) were male, and 135 (65.9%) had an average weight of more than 2 500 g. Moreover, most of them (63.9%) were born at term. Regarding the type of delivery, the most frequent mode of delivery was emergency cesarean section (n=113, 55.1%). Furthermore, 77% of recruited newborns presented with maternal risk factors; PROM was the most common risk factor identified (n=97, 41.8%), followed by preterm (n=61, 26.3%). There was a significant association between the development of neonatal sepsis and PROM (P=0.021). However, there was no association between neonatal sepsis and weight (P=0.94) and between neonatal sepsis and gestational age (P=0.81).

Altogether, 79.0% of neonates had first blood culture, of which 80.9% showed no bacterial growth. In addition, 58.0% had a second blood culture, and most of them (80.7%) showed no bacterial growth. CRP was performed in 78.0% of neonates, among which 38.8% were positive. A significant association was found between the first blood culture and CRP (P=0.046). *S. aureus* was the most common isolated pathogen in the first blood culture test (32.3%), while methicillin-resistant *Staphylococcus aureus* (MRSA) was the most common pathogen in the second blood culture test (39.1%) (Table 2). Sensitivity results for the isolated bacteria showed that both *S. aureus* and MRSA were sensitive to vancomycin (Table 3).

Regarding the selection of antibiotics, all neonates were firstly treated with a combination of cefotaxime and vancomycin, after that, 23.4% of the patients changed to other antibiotics, of which the combination of amikacin and meropenem was the most used antibiotics (n=33, 68.6%), followed by meropenem and vancomycin (n=6, 12.5%), and the remaining treated with other combination containing ciprofloxacin and imipenem.

Table 1. Demographic and clinical characteristics of the patients (*n*=205).

Demographic and clinical parameters	*N*	Percentage (%)
Gender		
Male	127	62.0
Female	78	38.0
Age		
One day	187	91.2
Two days	12	5.9
Three days	6	2.9
Neonatal weight		
Less than 1 500 g	13	6.3
1 500-2 500 g	57	27.8
More than 2 500 g	135	65.9
Maturity		
Preterm	67	32.7
Term	131	63.9
Post-term	7	3.4
Type of delivery		
Normal vaginal delivery	75	36.6
Emergency caesarian section	113	55.1
Elective caesarian section	17	8.3
Hospitalization period		
1-7 d	110	53.7
8-14 d	57	27.8
15-21 d	23	11.2
More than 21 d	15	7.3
Duration of antibiotics treatment		
Less than 7 d	116	56.6
7-13 d	79	38.5
14-21 d	10	4.9
Outcomes		
Discharge against medical advice	43	21.0
Death	4	2.0
Discharge	153	74.6
Refer	5	2.4
Type of risk factors		
Vaginal discharge	7	3.0
Maternal infection	12	5.2
Meconium aspiration syndrome	20	8.6
Low body weight	35	15.1
Pre-term	61	26.3
Rupture of membranes	97	41.8

Table 2. Distribution of patients according to isolated pathogens from blood culture test.

Isolated pathogens	Blood culture test	
	First (*n*=31)	Second (*n*=23)
Klebsiella	4 (12.9%)	4 (17.4%)
MRSA	9 (29.0%)	9 (39.1%)
Pseudomonas aeruginosa	8 (25.8%)	7 (30.4%)
Staphylococcus aureus	10 (32.3%)	3 (13.0%)

MRSA: Methicilin resistant *Staphylococcus aureus*.

4. Discussion

Neonatal sepsis shows a high mortality in developing countries, particularly after the emergence of bacterial resistance[17]. In this study, about 40% were diagnosed as sepsis, and 60% were given prophylaxis antibiotics for suspected infection. Other developing countries in Africa and Asia shows a comparable incidence of sepsis to the current study[6,18,19]. In this study, males represented 68% of the total samples, which agrees with a study done in Ghana[20], and with a national study carried out in Dr. Jafar Ibn Auf Pediatric Hospital[21].

The distribution of the neonatal terms in this study was that 32.7% were preterm neonates, 63.9% were term neonates and 3.4% were post-term neonates. The majority in our study were term neonates in contrast to most of the other studies, in which preterm neonates were more susceptible to sepsis due to the decreased level of IgM and IgA at birth[22,23]. This may be due to the prophylactic antibiotics given to most neonates for suspected infection in our study. In addition, our study is similar to a study carried in Soba University Hospital, where the majority of neonates with suspected or proven infection were term (37.1%)[24].

The most common risk factor was PROM which refers to the rupture of membrane lasting for 18 h or earlier than delivery. As an anatomical and physical barrier, the membrane can protect the uterus from vaginal infection and the risk of chorioamnionitis[25,26].

Table 3. Sensitivity of the isolates from the first and second blood cultures to different antibiotics.

Antibiotics	*Klebsiella*				MRSA				*Pseudomonas aeruginosa*				*Staphylococcus aureus*			
	First		Second		First		Second		First		Second		First		Second	
	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R
Carbapenems	3	1	3	1	-	-	-	-	7	1	7	0	-		-	-
Ciprofloxacin	2	2	2	2	-	-	-	-	4	4	3	4	1	9	-	-
Amikacin	4	0	3	1	-	-	4	5	7	1	5	2	-		-	-
Vancomycin	-	-	-	-	9	0	9	0	-	-	-	-	10	0	3	0
Clindamycin	-	-	-	-	2	7	2	7	-	-	-	-	1	9	1	2
Cotrimoxazole	-	-	-	-	1	8	-	-	-	-	-	-	-		-	-
Tetracyclin	-	-	-	-	2	7	1	8	-	-	-	-	-		-	-
Gentamycin	-	-	1	3	-	-	-	-	1	7	1	6	1	9	-	-

MRSA: Methicilin resistant *Staphylococcus aureus*. *S: Sensitive; R: Resistant.*

This study is slightly different from a study carried out in Khartoum North Teaching Hospital, which showed that the common risk factors are PROM, low birth weight, maternal fever, and hospital delivery, respectively[27]. Our study also showed a significant association between neonatal sepsis and PROM (P=0.021) which agrees with a study carried out in Pakistan[28]. Neither weight nor gestational age was found to be associated with neonatal sepsis (P=0.94 and 0.81, respectively). However, low birth weight and preterm are risk factors for sepsis. A significant association was found between first blood culture and positive CRP results (P=0.046), which agrees with the study conducted in Soba University Hospital in which the P-value was 0.019[24].

First blood culture was requested in only 160 neonates and this may result from poor documentation rather than poor practice. A total of 32.3% had bacterial growth of *S. Aureus* that is the most common isolated organism in the first test. Regarding the sensitivity of the isolated pathogens to different antibiotics, *S. aureus* and MRSA were more sensitive to vancomycin, and *Pseudomonas aeruginosa* was equally more sensitive to amikacin and carbapenems, but *Klebsiella* was more sensitive to amikacin. On the other hand, the second blood culture results were different from those of the first blood culture in that 39.1% had bacterial growth of MRSA that is the most common isolated pathogen, while *S. aureus* is the least common isolated pathogen (13.0%). The sensitivity of the isolated pathogens to different antibiotics was similar to the first culture results, except that *Pseudomonas aeruginosa* was more sensitive to carbapenems than amikacin. The result of this study agrees with the study carried out in Dr. Jafar Ibn Auf Pediatric Hospital, in which the most common isolated pathogen was *S. aureus*[21]. Similarly, a study carried out in Iran shows the most common isolates were gram-positive cocci, and the most effective antibiotic was vancomycin[29]. In addition, an Indian study shows *S. aureus* was more sensitive to vancomycin[30]. This suggests that the majority of EOS infections are caused by gram-positive organisms, especially *S. aureus*, which is the major normal flora located on the skin and could be transmitted by handling. Therefore, the techniques for infection control are essential (*e.g.*, hand washing). In contrast to all the above studies, a study conducted in Jordan shows that gram-negative pathogens were predominant in NICU[31].

Regarding the selection of empirical antibiotics in Saad Abul-Ella Teaching Hospital, the major applied antibiotic regimen was cefotaxime plus vancomycin, which is different from the recommended antibiotic, and the reason may be that isolated pathogens were usually resistant to first-line drugs (personal communication). This agrees with the study conducted in Dr. Jafar Ibn Auf Pediatric Hospital, in which the most used antibiotic regimen was cefotaxime plus vancomycin but with less percentage[21]. According to the result of this study, all pathogens had no or low sensitivity to gentamycin which is the recommended first-line drug according to most international guidelines. Tewari *et al.* showed that as there is an increasing prevalence of community extended-spectrum beta-lactamase producers as the causative organism of EOS, and the combination of ampicillin and gentamycin may not be the suitable empirical therapy[32]. Extended-spectrum beta-lactamase pathogens (*e.g.*, *E. coli* and *Klebsiella*) are associated with long hospital stays, broad-spectrum antibiotics, exposure to invasive devices, and low birth weight[33].

In developing countries, antibiotic resistance to community-acquired and hospital-acquired infections is very high. This high resistance levels force physicians to prescribe broad-spectrum antibiotics, like carbapenems and vancomycin as first-line regimens[7]. Ampicillin, which is the first-line drug, showed low sensitivity to isolated pathogens in several studies[34,35]. In a study conducted in Ghana, the isolated pathogens had shown 100% resistance to ampicillin[20]. In contrast to another study conducted in Tanzania, penicillin plus gentamicin was effective in the prevention of EOS[6].

According to Saad Abul-Ella Teaching Hospital practice, any preterm delivery (<37 weeks) or prolonged rupture of the membrane more than 18 h, the baby should receive empirical prophylaxis antibiotics, and blood culture should be done before starting antibiotics[36]. This antibiotics regimen should be changed to amikacin+meropenem if the blood culture result is negative and the patient's condition is not improved. And other antibiotics should be considered depending on the blood culture results (the sensitivity of isolated pathogens to different antibiotics). In this study, only about 23% of treated samples with empiric antibiotics were changed, most commonly to the combination of amikacin and meropenem. On the other hand, 74.6% of neonates were discharged in good condition. Notably, all of the 2.0% who died were from the probable sepsis group. This result is comparable with that of a study carried in Ethiopia in which the majority (84%) were discharged in good condition[26].

In conclusion, this study showed that the common risk factors for EOS were PROM, preterm and low birth weight. The major empiric antibiotics regimen use for EOS management in Saad Abul-Ella Teaching Hospital was cefotaxime plus vancomycin, and the most common pathogen associated with EOS was *S. aureus*.

Conflict of interest statement

The authors report no conflict of interest.

Authors' contribution

S.H.M developed the design and definition of the intellectual content, carried out the data collection and acquisition. R.R.B performed the analytic calculations and performed the data analysis. Both S.H.M and R.R.B authors contributed to the final version of the manuscript. B.A.Y supervised the project, designed the study, determined the concept, prepared and edited the final manuscript.

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