Journal of Infection and Public Health 12 (2019) 666–672

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Characteristics of neonatal Sepsis at a tertiary care hospital in Saudi Arabia

Abdulrahman Al-Matary[a,*], Humariya Heena[b], Ayah S. AlSarheed[b], Wafa Ouda[c], Dayel A. AlShahrani[a,b], Tariq A. Wani[a,b], Mostafa Qaraqei[a,b], Amani Abu-Shaheen[b]

[a] Neonatal Intensive Care Unit, King Fahad Medical City, Critical Care Services Administration, Riyadh, Saudi Arabia
[b] Research Center, King Fahad Medical City, Riyadh, Saudi Arabia
[c] Pharmacy Administration, King Fahad Medcial City, Riyadh, Saudi Arabia

ARTICLE INFO

Article history:
Received 4 December 2018
Received in revised form 3 March 2019
Accepted 11 March 2019

Keywords:
Neonatal sepsis
Neonatal intensive care unit
Saudi Arabia

ABSTRACT

Aim: To identify the risk factors, laboratory profile, microbial profile, mortality and complications, mortality causing organisms and antimicrobial susceptibility patterns of neonatal sepsis at a tertiary care hospital.

Methods: A retrospective study was conducted using the neonatal intensive care unit (NICU) database in King Fahad Medical City (KFMC), Riyadh, Saudi Arabia. All neonates born in KFMC with clinically diagnosed sepsis in the NICU were included in this study.

Results: During the study period, a total of 245 neonates with a culture-proven diagnosis of neonatal sepsis were included in this study and 298 episodes of sepsis were observed. Out of the 298 episodes, EOS occurred 33 (11.1%) times, and LOS occurred 265 (88.9%) times. For both neonates with EOS and LOS prematurity was the major neonatal risk factors for sepsis 16 (48.5%), 214 (80.8%); respectively. Multiparty and delivery by caesarean section were the top maternal risk factors of both EOS and LOS. Nneonates with LOS had high CRP, Total WBC count and thrombocytopenia compared to EOS neonates. Our results showed that in the EOS neonates, GBS was the most common pathogen followed by *Escherichia Coli.* In LOS neonates, the common organisms were *Staphylococcus* spp., *Klebsiella* and *Pseudomonas aeruginosa*. Mortality rate of neonatal sepsis is higher in EOS 5 (15.2%) from total EOS compared to LOS 24 (11.3%) from total LOS. All Gram-negative bacteria were sensitive to Amikacin. Gram-negative non-fermenting bacteria, such as *P. aeruginosa* and *Acinetobacter* were sensitive to amikacin and gentamycin. All Gram-positive bacteria were sensitive to gentamycin. Among thirteen *Candida albicans* isolates, 85% were sensitive to fluconazole.

Conclusion: Concerted efforts are needed to determine the spectrum of risk factors and the clinical characteristics of EOS and LOS in order to implement appropriate treatment strategies as sepsis remains to be a serious danger to neonatal wellbeing. Moreover, our study emphasizes that use of aminoglycosides is much agreeable as compared to the broad spectrum antibiotics which are more rampantly used nowadays.

Introduction

Neonatal sepsis is the term used to define any systemic bacterial infection with positive blood culture in the first month of life [1]. Neonatal sepsis is classified as early or late according to the age of onset during the neonatal period [2]. Although improvements in neonates' care have increased survival, sepsis is still one of the leading causes of mortality and morbidity among neonates, particularly in developing countries [3–5]. The incidence of neonatal bacterial sepsis may vary from one country to another as well as within the same country. In developing countries, neonatal mortality resulting from all different causes is approximately 34 per 1000 live births, occurring mainly in the first week of life, whereas it is only 5 per 1000 live births in developed countries [6].

* Corresponding author.
E-mail addresses: aalmatary@kfmc.med.sa (A. Al-Matary), hmunshi@kfmc.med.sa (H. Heena), ayah376@gmail.com (A.S. AlSarheed), wcafege@kfmc.med.sa (W. Ouda), daalshahrani@kfmc.med.sa (D.A. AlShahrani), tawani@kfmc.med.sa (T.A. Wani), mqaraqei@kfmc.med.sa (M. Qaraqei), aabushaheen@kfmc.med.sa (A. Abu-Shaheen).

https://doi.org/10.1016/j.jiph.2019.03.007

The risk factors for neonatal bacterial sepsis are multidimensional, ranging from maternofetal infection to the physical and cellular defense mechanisms of the neonate [7].

Group B streptococcus (GBS) has been reported to be the most frequent etiological agent of early-onset neonatal sepsis in developed countries, with high morbidity and mortality along with other microorganisms, depending on the microorganisms and the interrelated environmental, socioeconomic and hygienic factors [8]. A study conducted in 2013 at King Abdel Aziz Specialist Hospital in Taif, Saudi Arabia, found that *Klebseilla* spp. was one of the most common organisms causing late-onset sepsis in newborns [9].

Prognosis is mainly dependent upon the type of the microorganism, onset of sepsis, site of infection and related risk factors for sepsis. These factors may be different in each neonatal intensive care unit (NICU) or may vary in the same NICU over time. Accurate monitoring and evaluation of these factors are vital to improve prognosis and reduce mortality in neonatal sepsis. In Saudi Arabia, there are lack of recent studies that describing the epidemiology profile of neonatal sepsis in NICU. Thus, the aims of this study were to characterize the risk factors, hematology profile, microbial profile, mortality and complications, mortality causing organisms and antimicrobial susceptibility patterns of neonatal sepsis at a tertiary care hospital.

Materials and methods

Study design

A retrospective study was conducted using the database available at NICU of King Fahad Medical City (KFMC) in Riyadh, Saudi Arabia. The records available between January 2011 and December 2015 were reviewed during the study period. Our neonatal intensive care unit has 27 beds level III and 17 beds level II. The unit has infection control committee and full time infection control nurse from infection control department.

Study population

All neonates (0–28 days of age) born in KFMC with clinically diagnosed sepsis and confirm by blood culture in the NICU were included in this study. For neonates with coagulase negative *Staphylococcus*, additional clinical signs were utilized to distinguish contamination from true infection.

During the study period, a total of 245 neonates with a culture-proven diagnosis of neonatal sepsis were included in this study and 298 episodes of sepsis were observed. Out of the 298 episodes, EOS occurred 33 (11.1%) times, and LOS occurred 265 (88.9%) times.

The definitions of neonatal sepsis vary according to neonatal perinatal medicine [10] and the 2014 WHO protocol, wherein it is categorized as either early-onset sepsis (EOS), which occurs in the first 72 h of life, or late-onset sepsis (LOS), which occurs after 72 h of life. EOS is mainly due to organisms acquired before and during delivery, while LOS is due to organisms acquired after delivery and is mainly referred to as a healthcare-associated infection (HAI). LOS is a frequent complication of prolonged stay in the NICU following preterm birth.

Data collection

The following data were collected for neonates: (i) neonatal risk factors, which include gender, maturity, birth weight, Apgar score, central line catheter insertion and total parenteral nutrition (TPN); (ii) maternal risk factors, including antenatal care, type of gestation, parity, mode of delivery, and complications, such as preeclampsia, premature rupture of member (PROM), fever, antibiotic use during the intrapartum period, antepartum hemorrhage (APH), GBS, intrauterine growth restriction (IUGR), and steroids use; (iii) hematology profile (blood culture, C-reactive protein (CRP) (ng/ml), platelet count ($<100 \times 10^9$/l), total white blood cells (TWBCs, 10^3 cells/μl) and absolute neutrophil count (%)); (iv) microbial profile which showed the types of isolated organisms; (v) mortality and complications of neonatal sepsis; (vi) mortality causing organisms; and (vii) antimicrobial susceptibility patterns in all isolates.

Ethical considerations

Ethics approval was obtained from the Institutional Review Board at KFMC.

Statistical analysis

Statistical analyses were performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as the mean ± SD. Categorical variables were presented as frequencies with corresponding percentages. The number of episodes of sepsis were considered in analyzed the data.

Results

Neonatal and maternal risk factors of sepsis were summarized in Table 1. The mean birth weight was 2187.3 ± 964.1 g for a neonate with EOS and 1501.1 ± 876 g for a neonate with LOS. Moreover, the mean duration of hospital stay was 21.8 ± 34.3 days for neonates with EOS and 56.3 ± 58.4 days for neonates with LOS.

Neonatal risk factors

For neonates with EOS prematurity 16 (48.5%), low Apgar score at 1st minute 16 (48.5%), and male gender 15 (45.5%) were major neonatal risk factors for sepsis. In LOS, TPN 202 (76.2%), central catheterization 174 (65.7%) and low birth weight (<1500 g) 161(60.8%) were found to be the major risk factors besides prematurity 214 (80.8%) (Table 1).

Table 1
Neonatal and maternal risk factors of sepsis.

	Early onset of sepsis n (33)	Late onset of sepsis n (265)	p-Value
Neonatal factors			
Male gender	15(45.5)	153(57.7)	0.18
Prematurity	16(48.5)	214(80.8)	**<0.001**
Low birthweight (<1500 g)	9(27.3)	161(60.8)	**<0.001**
Low Apgar score at 1st minute	16(48.5)	155(58.5)	0.273
Low Apgar score at 5th minute	2(6.1)	30(11.3)	0.357
Central line catheter	12(36.4)	174(65.7)	**<0.001**
TPN	12(36.4)	202(76.2)	**<0.001**
Maternal factors			
Irregular antenatal care	8(24.2)	99(37.4)	0.139
Multiple gestation	4(12.12)	87(32.8)	0.081
Multipara	21(63.6)	206(77.7)	0.073
Caesarean section delivery	13(39.4)	149(56.2)	0.067
Pre-eclampsia	1(3.0)	10(3.8)	0.831
PROM	4(12.1)	30(11.3)	0.892
Intrapartum period			
Fever	4(12.1)	4(1.5)	**<0.001**
APH	1(3.0)	16(6.0)	0.482
GBS	4(12.1)	5(1.9)	**0.013**
IUGR	4(12.1)	29(10.9)	0.839

TPN: Total parenteral nutrition; CRP: C-reactive protein; PROM: premature rupture of member; APH: antepartum hemorrhage; GBS: Group B streptococcus; IUGR: intrauterine growth restriction.
Data are presented as number and percentage.
Bold values are less than 0.001.

Maternal risk factors

Multiparty and delivery by caesarean section were the top maternal risk factors of both EOS and LOS. About, 12% of mothers with either premature rupture of the membranes (PROM) or Group B streptococcus (GBS) infection had babies with EOS. Moreover, 12.1% of the mothers had a history of fever, 33.3% of them had used antibiotics during the intrapartum period and 8 (24.2%) had used steroids. Regarding maternal risk factors, in LOS a mere 1.9% had GBS, 12.5% had used antibiotics during intrapartum period and 86 (32.5%) had used steroids (Table 1).

A significant difference was found between LOS and EOS and some of the neonatal and maternal risk factors of sepsis: prematurity ($p < 0.001$), low birthweight (<1500 g) ($p < 0.001$), TPN ($p < 0.001$), intrapartum period fever ($p < 0.001$) and GBS ($p = 0.013$)

Table 2
Hematology profile of the study subjects.

	Early-onset sepsis n (%)	Late-onset sepsis n (%)	p-Value
High CRP (ng/ml)	11(33.3)	162(76.4)	**<0.001**
Thrombocytopenia $<100 \times 10^9$/l	4(12.9)	75(35.4)	**0.003**
Total white blood cells (TWBCs/10^3 cells/μl)			
<5000 (Low)	8(25.8)	20(9.4)	
5000–20,000 (Normal)	19(61.3)	141(66.5)	0.109
>20,000 (High)	4(12.9)	49(23.1)	
Absolute neutrophil count (%)			
≤1000	5(15.2)	29(13.7)	0.107

Bold values are less than 0.001.

Hematology profile

Eleven (33.3%) patients with EOS showed high levels of CRP, while equal number, i.e., 4 (12.9%) of the babies showed either increased white blood cells count >20,000 (TWBCs/ 103 cells/μl) or thrombocytopenia and 8 (25.8%) had low TWBC counts $<5 \times 10^3$ cells/μl and 5 (15.2%) showed neutropenia on peripheral blood film. The majority 162 (76.4%) of neonates with LOS showed high CRP levels ($p < 0.001$), 75 (35.4%) of them had thrombocytopenia, 49 (23.1%) had increased white blood cells count >20,000 (TWBCs/103 cells/μl), 20(9.4%) had low TWBC counts $<5 \times 103$ cells/μl and 29 (13.7%) had absolute neutrophil count ≤1000 (%) (Table 2).

A significant difference was found in CRP levels ($p < 0.001$) and Thrombocytopenia ($p = 0.003$) between EOS and LOS and.

Microbial profiles

Amongst neonates with EOS, GBS (11, 33.3%) was the most frequently detected pathogen followed by *Escherichia Coli* (*E. Coli*) (9, 27.3%) (Fig. 1). Whereas, among LOS neonates, the common causative organisms were *Staphylococcus* spp. (126, 59.4%), *Klebsiella* (37, 17.5%) and *Pseudomonas aeruginosa* (*P. aeruginosa*) (21, 9.9%) (Fig. 2).

Regarding the prevalence of fungal infections among neonates with EOS, no cases were discovered; while 20 (0.6%) neonates with LOS had Candida infection, with a total of 22 episodes. Candida albicans was the most common etiological species (14, 63.6%) followed by Candida parapsilosis (4, 18.2%) (Fig. 3).

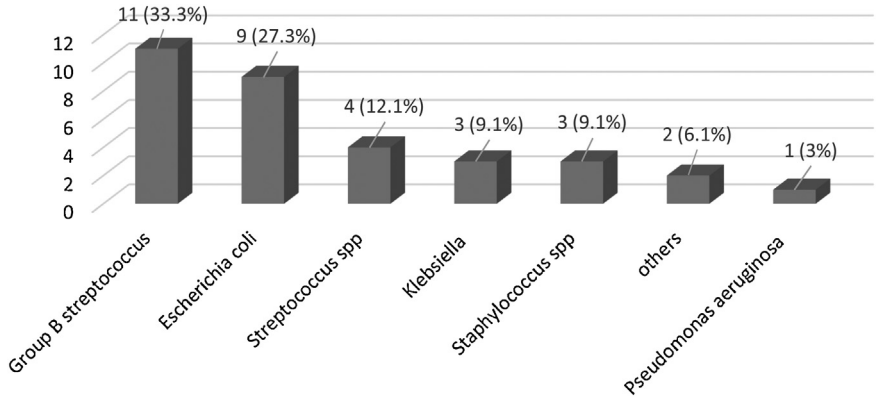

Fig. 1. Organisms in early-onset sepsis.

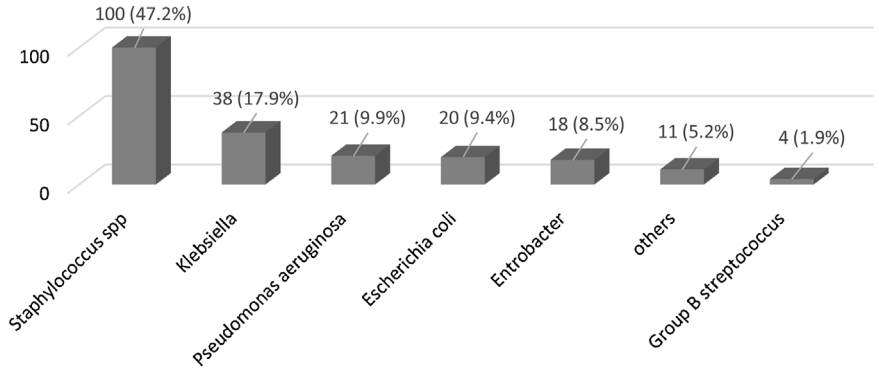

Fig. 2. Organisms in late-onset sepsis.

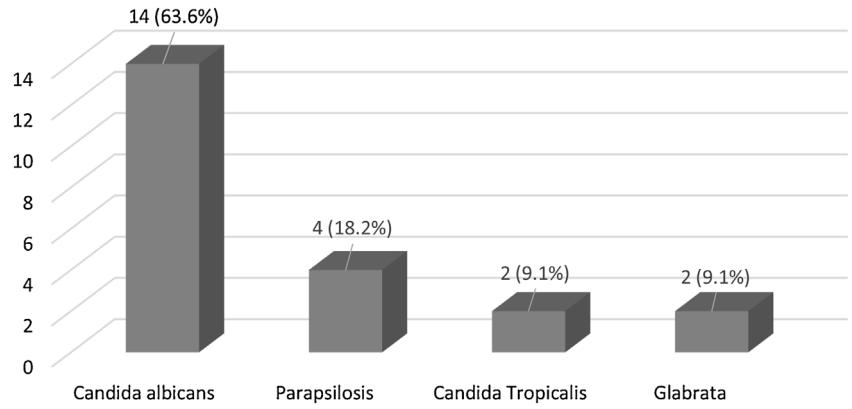

Fig. 3. Fungal sepsis.

Table 3
Mortality and complications of neonatal sepsis.

	Early-onset sepsis n (%)	Late-onset sepsis n (%)	p-Value
Mortality	5(15.2)	24(11.3)	0.176
CLD	0(0.0)	126(59.4)	**<0.001**
Extended length of stay >120 days	4(12.1)	113(53.3)	**<0.001**
IVH	4(12.1)	26(12.1)	0.908
NEC	1(3.0)	63(23.8)	**0.006**
ROP	0(0.0)	16(7.5)	0.093
VAP	0(0.0)	37(17.5)	**0.004**

CLD: chronic lung disease; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; and VAP: ventilator-associated pneumonia.
Bold values are less than 0.001.

Table 4
Organisms isolated in cases of death.

Organism	Early-onset sepsis n (%)	Late-onset sepsis n (%)
Gram-negative	5 (15.2)	19 (9)
Gram-positive	0 (0)	3 (1.4)
Candida	0 (0.0)	2 (0.94)

Mortality and complications of neonatal sepsis

Among EOS neonates, 5 (15.2%) died from Gram-negative bacterial infection, 4 (12.1%) of the neonates had an extended length of stay >120 days or suffered intraventricular haemorrhage (IVH). Whereas, among LOS, 24 (11.3%) died. Chronic lung disease (CLD) was the most prevalent complication of neonatal sepsis (126, 59.4%) followed by extended length of hospital stay >120 days 113 (53.3%) and NEC 63 (23.8%) (Table 3).

A significant difference was found between EOS and LOS and the following complications of neonatal sepsis: CLD ($p < 0.001$), Extended length of stay >120 days ($p < 0.001$), NEC ($p = 0.006$) and VAP ($p = 0.004$).

Organisms causing mortality

Gram-negative organisms were the leading cause of death in neonates with EOS and LOS. In EOS, the only organisms causing mortality that were isolated from the 5 (15.2%) neonates who died were Gram-negative bacteria, whereas in LOS, the most frequent organisms causing mortality isolated were Gram-negative bacteria 19 (9%) followed by Gram-positive bacteria (3, 1.4%) and *Candida* 2 (0.94%) (Table 4).

Amongst neonates with EOS, *E. coli* was isolated in 3 cases as the organism causing mortality, and *Klebsiella* and *P. aeruginosa* were isolated in 2 cases. Among neonates with LOS, the most common organism causing mortality was *P. aeruginosa* in 8 cases followed by *E. coli* in 4 cases.

Antimicrobial susceptibility

All microbial organisms were tested with the recommended antibiotics. We reviewed all positive blood cultures and sensitivity patterns to antibiotics. Streptococci species was sensitive to Timethoprim–Sulfamethotazole (Bactrim). All Gram-negative bacteria were sensitive to Amikacin. Gram-negative non-fermenting bacteria, such as *P. aeruginosa* and *Acinetobacter* were sensitive to amikacin and gentamycin. All Gram-positive bacteria were sensitive to gentamycin. Among thirteen *C. albicans* isolates, 85% were sensitive to fluconazole (Tables 5–8).

Discussion

This study is one of the largest reported from a tertiary care center in Saudi Arabia to depict the organism profile along with the antimicrobial sensitivity pattern, risk factors and clinical characteristics of neonatal sepsis. We had a total of 3437 neonates admitted to the NICU from January 2011 to the end of December 2015. Out of the 298 culture-proven episodes, 245 neonates were diagnosed with neonatal sepsis; 33 had EOS, and 212 had LOS, which is consistent with reports from other studies that the number of neonates presenting with LOS are considerably greater than the number of neonates with EOS [12–14].

Neonates with very-low birth weights are more likely to have sepsis, as are those with depressed respiratory function at birth and maternal risk factors [1]. In our study, neonatal sepsis occurred mainly due to prematurity. We found that 48.5% of EOS neonates were premature, while 78.3% of the neonates with LOS were premature, which is in agreement with the findings by a previous study by Graham et al. [15] and Greenberg et al. [16]. These findings may be attributed to the poor host defenses of premature newborns, who are thus more likely to suffer from neonatal sepsis. EOS occurs in utero secondary to maternal hematogenous infection or, more often, chorioamnionitis and aspiration of infected amniotic fluid or secretions in the birth canal leading to pneumonia and sepsis manifested by fetal distress or neonatal asphyxia [11].

LOS occurs after 72 h of life and is acquired from the caregiving environment. The skin, respiratory tract, conjunctiva, gastrointestinal tract, TPN line and umbilicus of the neonates may become colonized from the environment, and such colonization leads to the possibility of LOS from invasive microorganisms. Vectors for

Table 5
Antimicrobial susceptibility of Gram-negative bacteria.

Isolates tested	Isolate tested (n)	Antibiotics									
		Ampicillin	Ceftazidem	Cefotaxim	Cefepime	Gentamycin	Amikacin	Timethoprim–Sulfametho-tazole	Pipracillin–Tzobactam	Imepenem	Meropenem
Escherichia coli	29	14%	59%	62%	62%	62%	100%	48%	86%	100%	100%
Klebsiella	40	0%	85%	83%	83%	83%	98%	83%	95%	100%	100%
Enterobacter species	18	6%	67%	61%	83%	83%	100%	89%	78%	100%	100%
Serratia marcescens	3	0%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Citrobacter koseri	1	0%	100%	100%	100%	100%	100%	100%	100%	100%	100%

Table 6
Antimicrobial susceptibility of Gram-negative non-fermenting bacteria.

Isolates tested	Isolate tested (n)	Antibiotics							
		Ceftazidem	Cefepime	Pipracillin–Tzobactam	Gentamycin	Amikacin	Imepenem	Meropenem	Timethoprim–Sulfamethotazole
Pseudomonas aeruginosa	22	77%	100%	100%	100%	100%	91%	91%	Not done
Acinetobacter	6	67%	67%	50%	67%	67%	67%	67%	17%
Stenotophonomanas	1	0%	—	—	—	—	—	—	100%
Stenotro. maltophilia	1	0%	—	—	—	—	—	—	100%

— = Not tested for other antibiotics.

Table 7
Antimicrobial susceptibility of Gram-positive bacteria.

Isolates tested	Isolate tested (n)	Antibiotics			
		Penicillin	Ampicillin	Timethoprim–Sulfamethotazole	Vancomycin
Staph aureus	8	—	—	88%	100%
Staphylococcus species	111	—	—	53%	100%
Enterococcus faecalis	6	—	83%	—	100%
Streptococci species	4	75%	75%	100%	100%
Group B streptococcus	15	100%	—	—	100%

— = Not tested for antibiotics.

Table 8
Antimicrobial susceptibility of Fungi.

Candida	Isolate tested (n)	Anti-fungal						
		Fluconazole	Itraconazole	Amphotericin B		Ketoconazole	Voriconazole	Caspofungin
				Sensitive	nbp[a]			
Candida glabrata	2	50%	0%	50%	50%	—	50%	100%
Candida parapsilosis	5	80%	80%	20%	80%	20%	80%	60%
Candida tropicalis	2	100%	100%	0%	100%	—	100%	100%
Candida albicans	13	85%	69%	85%	15%	15%	85%	92%

— = Not tested for antibiotics.
[a] No break point: as per clinical and laboratory standards institute guidelines for antimicrobial susceptibility testing.

such colonization may include vascular or urinary catheters, other indwelling lines, or contact with caregivers who had a previous bacterial infection [17]. In our study, TPN line, central catheterization, and very-low birth weight (<1500 g) were found to be major risk factors in addition to prematurity among neonates with LOS. Considerable evidence from the literature shows that TPN is associated with blood stream infections, which are potentially fatal complications with a mortality rate of 11% in neonates [18].

Furthermore, regarding the neonatal risk factors for LOS, our results revealed that the majority of patients were male (59.4%). In a study conducted by Purtilo et al. [19] it was found that males have a higher incidence of neonatal sepsis, possibly due to defects in X-linked immunoregulatory genes.

KFMC is a tertiary referral care hospital with a number of facilities to treat high-risk neonates who are susceptible to infection. However, in our study, we found certain factors, such as a low Apgar score, in a significant number of neonates: 48.5% in EOS, and 58.5% in LOS, which is consistent with previous studies that have reported that low Apgar score is significantly associated with neonatal sepsis [12,13]. Neonates with low Apgar scores are more prone to infection, as they are less likely to cope with external stressors [14,20]. Additionally, the results showed that 60.8% of neonates with low birth weight (<1500 g) had LOS and 27.3% had EOS which is in agreement with the finding from an earlier study by Haque [21].

Multiparty and delivery by caesarean section were found to be the top maternal risk factors of both EOS and LOS. Similarly, a study conducted by Al Dasoky et al. on 60 neonates at tertiary care hospital in Jordan, reported delivery by caesarean section as the highest maternal risk factors of neonatal sepsis [22].

EOS occurs in utero, secondary to maternal hematogenous infection or, more often, chorioamnionitis and aspiration of infected amniotic fluid or secretions in the birth canal leading to pneumonia and sepsis manifested by fetal distress or neonatal asphyxia [13]. Only 12.1% of the neonates with EOS had GBS in our study. This may be explained by the fact that 33.3% of the mothers had used antibi-

otics during the intrapartum period due to the increasing emphasis on the use of GBS intrapartum prophylaxis.

While the probability of sepsis is about 1% in the newborns whose mothers have (+) PROM, this rate increases to 4–6% in preterm newborns in the presence of PROM [23]. In the study of Gürsu, no statistical significance was found between the sepsis group and control group in terms of PROM [24]. In our study, PROM was positive in 12.1% of the patients with EOS and 11.3% of LOS patients.

In our study, the mothers of the neonates with EOS and LOS had used antibiotics during the intrapartum period (33.3%), (12.5%), respectively. Moreover, out study reported the use of steroids by the that the mothers of the neonates with EOS and LOS. A study conducted by Hornik et al. revealed that prenatal steroid and antibiotic usages were reported to be risk factors for EOS and LOS [5]. Appropriate maternal diagnosis and treatment are compulsory to diminish the neonatal morbidity and mortality linked with neonatal sepsis as neonatal sepsis may present with clinical signs which may make it difficult to establish the diagnosis and its outcome may be devastating.

CRP was positive in 33.3% of the patients with EOS in considerably higher number 84.1% in LOS. CRP is an indicator of acute phase response to inflammation and tissue damage. CRP has long been used as a precise measure of infection especially for neonates because the recognition of danger signs of sepsis in a neonate is extremely difficult and challenging [14,20]. CRP is an acute phase reactant which is used very frequently in the diagnosis of neonatal sepsis. CRP release starts 4–12 h after the onset of the infectious event, peaks in the 24th–60th h and its amount decreases when infection regresses [15,21].

Total WBC count is also a useful indicator of neonatal wellbeing and severity of the infection. Our study showed that approximately 94% of the neonates with LOS had high WBC count (>20,000) while only 12.9% of EOS neonates had high counts. Similarly, leucopenia (<5000) occurred in about 75% of the LOS neonates and 25.8% of EOS neonates. Leucopenia indicates that the neonate has an overwhelming infection. The higher infection rates in LOS may be explained by the fact that EOS occurs while the mother–child duo is still admitted in the hospital and is subsequently managed effectively in the hospital setting while in LOS there might have been a considerable delay in diagnosing the condition and seeking the treatment.

In the study of Topuz [25], the platelet count was found to be significant in the diagnosis of sepsis [7]. In our study, thrombocytopenia was found in 12.9% in neonates with EOS and 40.7% in neonates with LOS which indicated the significance of thrombocytopenia in sepsis.

The causative organisms of neonatal sepsis vary in developed and developing countries. Overall, Gram-negative organisms were isolated in 61.1% of cases, while Gram-positive, Gram-negative nonfermenting bacteria and yeast were isolated in 21.5%, 10.1% and 7.1% of cases, respectively. A study conducted by Bas et al. [26] indicated that Gram-negative bacteria were isolated at a rate of 70.8% and that Gram-positive bacteria were isolated at a rate of 22.6%. The predominance of Gram-negative organisms may be attributed to the current efforts toward maternal intrapartum antimicrobial prophylaxis against GBS [27].

Our results showed that in the EOS neonates, GBS was the most common pathogen followed by *E. Coli*. In LOS neonates, the common organisms were *Staphylococcus* spp., *Klebsiella* and *P. aeruginosa*. Our study showed that none of the neonates with EOS had *Candida* infections, while 20 neonates with LOS had *Candida* infections. The prevalence of *Candida* infections was 0.6% of total admissions during the study period. *C. albicans* was the most common pathogen followed by *C. parapsilosis*. A meta-analysis of 19 studies found that three of the four organisms (*Staphylococcus aureus* , *E. coli*, and *Klebsiella* species) caused nearly half (44%) of all infections in neonates [28]. However, Hyde et al. [29] reported that the most common etiologic agents in EOS were GBS, *E. coli*, and *Streptococcus viridian*, while CONS, *Staphylococcus aureus*, and *C. albicans* were the most common etiologic agents in LOS. In studies conducted in Western countries, the most commonly isolated agent in EOS is GBS followed by Gram-negative bacilli and staphylococci [30]. In the study by Gürsu [24], Gram-negative bacilli, staphylococci, and *Candida* were isolated in 52.9%, 41.1% and 5.9% of cases of EOS, respectively. Staphylococci were isolated in 75% and Gram-negative bacilli were isolated in 16.6% of neonates with LOS. In the study by Topuz [25], staphylococci, Gram-negative bacilli, GBS and *Streptococcus* spp. were isolated in order of frequency in neonates with EOS, and staphylococci and Gram-negative bacilli were isolated in order of frequency in neonates with LOS.

Consistent with our findings previous studies reported that the mortality rate of neonatal sepsis is higher in EOS compared to LOS [24,31]. A study conducted by Gürsu et al., the mortality rate in neonatal sepsis was found to be 21.4% in the neonates with EOS and 18.8% in the neonates with LOS [24]. In Esma et al. study, the mortality rate was found to be higher in the patients with EOS 10% compared to the patients with LOS 5% [31].

It is not easy to compare antibiotic susceptibility patterns between countries, as the epidemiological profile of neonatal sepsis is widely variable depending upon the use and ease of acquiring antibiotics over the counter [7]. In our study, among all Gram-negative isolates, we found that amikacin is effective in 98–100% of cases and all Gram-negative nonfermenting were highly sensitive towards both aminoglycosides (amikacin and gentamycin).

Through this study we aimed to elaborate on the prevailing strains and the antibiotic sensitivity patterns for neonatal sepsis in our hospital. Periodic evaluations through more extensive and prospective research are necessary to understand the temporal changes in the causative organisms and their antibiotic susceptibility.

This is one of few studies conducted in the Kingdom and is significant as it represents a 5-year comprehensive database analyzed to determine the risk factors, laboratory profile, microbial profile and antimicrobial susceptibility patterns and outcomes of neonatal sepsis at one of the most reputable tertiary health care institutions in KSA. However, the study limited in scope as it was conducted at a single center.

Conclusion

Neonatal sepsis occurred mainly due to prematurity, multiparty and delivery by caesarean section were found to be the top maternal risk factors of both EOS and LOS. Our results showed that GBS was the most common pathogen causing EOS among neonates, while *Staphylococcus* spp. was the most common organism among LOS neonates. Neonates with EOS had a higher mortality as compared to LOS. Moreover, our study emphasizes that use of aminoglycosides (amikacin and gentamycin) is much agreeable as compared to the broad spectrum antibiotics which are more rampantly used nowadays even in tertiary care hospital settings. In summary, concerted efforts are needed to determine the spectrum of risk factors and the clinical characteristics of EOS and LOS in order to implement appropriate treatment strategies as sepsis remains to be a serious danger to neonatal wellbeing.

Our study provides valuable insights documenting important factors that affect susceptibility and outcomes of neonatal sepsis which is a global public health issue. Research on neonatal sepsis is an innovative movement in the region with a need to assess the gravity of the problem at a national scale and we hope that our findings will stimulate further research in the field benefitting both the policy makers for crafting preventive strategies and the clinicians

for a better understanding about the magnitude of the disease in Saudi Arabia.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Not required.

References

[1] Naher H, Khamael A. Neonatal sepsis; the bacterial causes and the risk factors. Int Res J Med Sci 2013;1:19–22.
[2] Zahedpasha Y, Ahmadpour-Kacho M, Hajiahmadi M, Haghshenas M. Procalcitonin as a marker of neonatal sepsis. Iran J Pediatr 2009;19:117–22.
[3] Ovalı F. Bakteriyel enfeksiyonlar. In: Dağoğlu T, Ovalı F, editors. Neonatoloji. İstanbul: Nobel Tıp Kitabevleri; 2007. p. 765–810.
[4] Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928–2003. Pediatrics 2005;116:595–602.
[5] Hornik CP, Fort P, Clark RH, Watt K, Benjamin Jr DK, Smith PB, et al. Early and late onset sepsis in very-low-birth-weight neonates from a large group of neonatal intensive care units. Early Hum Dev 2012;88:S69–74.
[6] Costello A, Francis V, Byrne A, Puddephatt P. State of the world's newborns: a report from saving newborn lives. Washington, DC: Save the Children and Women and Children First; 2001.
[7] Jumah DS, Hassan M. Predictors of mortality outcome in neonatal sepsis. Med J Basrah Univ 2007;25:11–8.
[8] Motara F, Ballot DE, Perovic O. Epidemiology of neonatal sepsis at Johannesburg hospital. South Afr J Epidemiol Infect 2005;20:90–3.
[9] Al-Zahrani AK. Health care associated infection in neonatal intensive care unit of King Abdulaziz specialist hospital. Adv Infect Dis 2013;3:300–5, 3053.
[10] Edwards MS. Postnatal infections. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Neonatal perinatal medicine: diseases of the fetus and neonates. St Louis, MO: Mosby; 2006. p. 791–804.
[11] Satar M, Ozlu F. Neonatal sepsis: a continuing disease burden. Turk J Pediatr 2012;54:449–57.
[12] Jabiri A, Wella HL, Semiono A, Saria A, Protas J. Prevalence and factors associated with neonatal sepsis among neonates in Temeke and Mwananyamala Hospitals in Dar es Salaam, Tanzania. Tanzan J Health Res 2016;18:1–7.
[13] Sundaram V, Kumar P, Dutta S, Mukhopadhyay K, Ray P, Gautam V, et al. Blood culture confirmed bacterial sepsis in neonates in a North Indian tertiary care center: changes over the last decade. Jpn J Infect Dis 2009;62:46–50.
[14] Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics 1999;103:e77.
[15] Graham 3rd PL, Begg MD, Larson E, Della-Latta P, Allen A, Saiman L. Risk factors for late onset Gram-negative sepsis in low birth weight neonates hospitalized in the neonatal intensive care unit. Pediatr Infect Dis J 2006;25:113–7.
[16] Greenberg D, Shinwell ES, Yagupsky P, Greenberg S, Leibovitz E, Mazor M, et al. A prospective study of neonatal sepsis and meningitis in Southern Israel. Pediatr Infect Dis J 1997;16:768–73.
[17] van den Hoogen A, Gerards LJ, Verboon-Maciolek MA, Fleer A, Krediet TG. Long-term trends in the epidemiology of neonatal sepsis and antibiotic susceptibility of causative agents. Neonatology 2010;97:22–8.
[18] Gaynes RP, Edwards JR, Jarvis WR, Culver DH, Tolson JS, Martone WJ. Nosocomial infections among neonates in high-risk nurseries in the United States. National nosocomial infections surveillance system. Pediatrics 1996;98:357–61.
[19] Purtilo DT, Sullivan JL. Immunological bases for superior survival of females. Am J Dis Child 1979;133:1251–3.
[20] Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol Rev 2014;27:21–47.
[21] Haque KN. Definitions of bloodstream infection in the newborn. Pediatr Crit Care Med 2005;6:S45–9.
[22] Al Dasoky HA, Al Awaysheh FN, Kaplan NM, Al Rimawi HA. Risk factors for neonatal sepsis in tertiary hospital in Jordan. J R Med Serv 2009;16:16–9.
[23] Geme Jr JW, Murray DL, Carter J, Hobel CJ, Leake RD, Anthony BF, et al. Perinatal bacterial infection after prolonged rupture of amniotic membranes: an analysis of risk and management. J Pediatr 1984;104(4):608–13.
[24] Gürsu HA. Yenidoğan sepsisi tanısında serum amiloid A (SAA)'nın önemi ve CRP ile karşılaştırılması. Uzmanlık Tezi. İstanbul: Dr. Lütfi Kırdar Kartal Eğitim ve Araştırma Hastanesi I. Çocuk Sağlığı ve Hastalıkları Kliniği; 2005.
[25] Topuz S. Yenidoğan sepsisinin tanı ve izleminde C-reaktif protein ile prokalsitonin değerlerinin karşılaş- tırılması. Nobel Medicus 2012;8:6–72.
[26] Bas AY, Demirel N, Zenciroglu A, Gol N, Tanir G. Nosocomial blood stream infections in a neonatal intensive care unit in Ankara, Turkey. Turk J Pediatr 2010;52:464–70.
[27] Schrag SJ, Zywicki S, Farley MM, Reingold AL, Harrison LH, Lefkowitz LB, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. N Engl J Med 2000;342:15–20.
[28] Egarter C, Leitich H, Karas H, Wieser F, Husslein P, Kaider A, et al. Antibiotic treatment in preterm premature rupture of membranes and neonatal morbidity: a metaanalysis. Am J Obstet Gynecol 1996;174:589–97.
[29] Hyde TB, Hilger TM, Reingold A, Farley MM, O'Brien KL, Schuchat A. Trends in incidence and antimicrobial resistance of early-onset sepsis: population-based surveillance in San Francisco and Atlanta. Pediatrics 2002;110:690–5.
[30] Gerdes JS. Diagnosis and management of bacterial infections in the neonate. Pediatr Clin North Am 2004;51:939–59.
[31] Turhan Esma Ebru, Gürsoy Tuğba, Oval Fahri. Factors which affect mortality in neonatal sepsis. Turk Pediatri Ars 2015;50:170–5, http://dx.doi.org/10.5152/TurkPediatriArs.2015.2627.