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THE PREDICTORS OF DEATH AMONG NEONATES WITH BLOOD CULTURE CONFIRMED SEPSIS

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ABSTRACT

Background: Neonatal sepsis is caused by a bacterial or fungal infection in the newborn's bloodstream. Symptoms include temperature instability, breathing difficulties, and refusal to eat. Neonatal sepsis is classified as either early-onset or late-onset. All levels of the health system must comprehend the diagnosis, etiology, and treatment of neonatal sepsis in order to guarantee the effective and long-term detection of this condition. **Objectives:** Is to identify the predictors of death among newborns with blood culture-proven sepsis at Ibin Al Atheer Teaching Hospital in Mosul, Iraq. **Methods:** A retrospective, descriptive cohort study of recorded data from the department of pediatric medicine at Ibin Al Atheer Teaching Hospital, from January 2023 to the end of December 2023. The questionnaire includes four parts; part one for socio-demographic information. Part two for specific clinical features associated with neonatal sepsis. Part three for maternal obstetric history. Part four for laboratory investigations used. In addition to that; Hospitalization outcomes were recorded as survival at discharge or passed (death). The total number of neonates determined was then separated into two groups. Group A comprised of neonates who survived until discharge, while Group B consisted of neonates who died while in the hospital. **Results:** The study includes 200 patients with neonatal sepsis admitted to Ibin Al Atheer Teaching Hospital during the period of the study, the mean age of the study patients is 5.43 ± 2.14 days. Males more predominant than females with ratio of 1.35:1. The study found that the mortality rate of neonatal sepsis is 41.5%. Statistically significant difference regarding the presence of lethargy (P value <0.001), vomiting (P value <0.001), respiratory distress (P value <0.001), leukocytes (P value <0.001), elevated blood sugar (P value = 0.029). Moreover; *Streptococcus species* founded to be significantly more among patients with late onset sepsis (P value = 0.037). **Conclusion:** High antibiotic resistance in Iraq can increase the overall mortality rate of infectious diseases. Moreover; Lethargy, vomiting, respiratory distress, leukocytosis and high random blood sugar are significantly association with death. Following strict protocols and prescribing antibiotics according to culture and sensitivity tests are recommended to all patients with infections regardless to the type and location of infection.

KEYWORDS: Antibiotic resistance, Mortality rate, Mosul, Iraq.

1- INTRODUCTION

Neonatal sepsis is caused by a bacterial or fungal infection in the newborn's bloodstream.[1] Symptoms include temperature instability, breathing difficulties, and refusal to eat.[2] Neonatal sepsis is classified as either early-onset (EOS) or late-onset (LOS). EOS is defined as the development of infection symptoms within 72 hours of life, which may or may not involve pathogen isolation. In LOS, signs and symptoms appear after 72 hours of life.[3-4]

Neonatal sepsis is a major worldwide health concern that has detrimental effects on health and quality of life in addition to causing large health burdens from lost productivity and medical costs.[5] Around 2.4 million newborn deaths annually, or 6,700 deaths per day, are attributed to sepsis, making it the leading cause of infant mortality.[6] Prompt diagnosis involves intensive supportive treatment, proper antibiotic prescription, and early diagnosis.[7] The risk of neonatal sepsis death is highest during the first 28 days of life, and children under 5 are highly susceptible to sepsis.[8]

A blood culture is the gold standard test for diagnosing newborn sepsis.[9] Neonatal sepsis that has been culture-proven occurs when there is pathogen isolation on blood

culture test or a positive PCR investigation in neonates with clinically neonatal sepsis.[9-10] All levels of the health system must comprehend the diagnosis, etiology, and treatment of neonatal sepsis in order to guarantee the effective and long-term detection of this condition.[11] The effectiveness of empirical treatment may be compromised by significant regional and temporal variations in the responsiveness to antibiotics.[12]

The prevalence of multi-drug resistance (MDR) infections is steadily rising in Iraq.[13] According to the Centers for Disease Control and Prevention (CDC), multi-drug resistance is the acquired resistance to at least one agent in three or more antimicrobial categories.[14] Implementing strict antibiotic stewardship programs can combat emerging infections' multi-drug resistance. Antibiotic stewardship focuses on identifying isolated culture-positive organisms and their antibiotic sensitivity patterns.[15]

This study aimed to identify the bacteriological profile and predictors of death among newborns with blood culture-proven sepsis at Ibin Al Atheer Teaching Hospital in Mosul, Iraq. This national hospital receives sick neonates from various health facilities across the country, making it a vital place to assess the effectiveness of drugs in battling newborn infections during the last few years.

PATIENTS AND METHODS

After obtaining ethical approval from the ethical committee of Nineveh Health directorate. A retrospective, descriptive cohort study of recorded data from the department of pediatric medicine at Ibin Al Atheer Teaching Hospital, from January 2023 to the end of December 2023.

The study included neonates who were admitted to the neonatal department, diagnosed with sepsis, and had positive blood cultures. Complete history was taken from all the patients by giving the parents a questionnaire form and a full physical examination was done to all the patients.

The questionnaire includes four parts; part one for socio-demographic data such as patients' age, sex, birth weight, gestational age at birth (<37 weeks considered premature), Apgar score at 5 min, place of delivery, mode of delivery. Part two for specific clinical features, such as jaundice, temperature instability (hypothermia, hyperthermia), respiratory distress, poor feeding, vomiting, convulsions, poor reflexes, pallor, jaundice, and umbilical redness. Part three for maternal obstetric history included PROM lasting over 24 hours, urinary tract infection, antibiotic use, and chorioamnionitis. Part four for laboratory investigations such as blood culture, hemoglobin, random blood sugar, white blood cells, platelets, and CRP levels. Anemia was defined as a hemoglobin level <10 g/dl, leucopenia as a total white blood count <5,000/mm^3, leukocytosis as a total white blood count >20,000/mm, and thrombocytopenia as a platelet count <150,000/mm^2. In addition to that; Hospitalization outcomes were recorded as survival at discharge or passed (death). The total number of neonates determined was then separated into two groups. Group A comprised of neonates who survived until discharge, while Group B consisted of neonates who died while in the hospital.

The study excluded both clinically suspected neonates with negative blood cultures and neonates with positive blood cultures but with incomplete or missing information. Moreover; the study excluded neonates who died during the first three days of delivery and those with blood cultures result of *Staphylococcus coagulase-negative* or *yeast* infections.

According to hospital policy, every patient has two blood samples drawn for blood cultures under aseptic circumstances from various peripheral venipuncture sites at intervals of 1/2 to 1 hour. About two to five milliliters of blood were drawn, stored in aerobic culture bottles, and sent to the hospital's Central Laboratory for processing. The first-line antibiotics ampicillin and gentamicin, as well as the second-line drugs ceftriaxone, vancomycin, and amikacin, were all subjected to antimicrobial sensitivity testing. The findings were classified as sensitive, moderate, or resistant. Isolates exhibiting moderate resistance were classified as resistant during data analysis.

Statistically analysis done by using SPSS 30.0 software application. To compare the means, the Student's t-test was employed. The p-value was considered statistically significant if it was less than 0.05 at 95% CI. The indicators that showed significant correlations with mortality were thought to be possible risk factors for a poor outcome in cases of neonatal sepsis. The odds ratio was calculated using risk estimate analysis using these variables.

3. RESULTS

The study includes 200 patients with neonatal sepsis admitted to Ibin Al Atheer Teaching Hospital during the period of the study, the mean age of the study patients is 5.43 ± 2.14 days. Males more predominant than females with ratio of 1.35:1. The majority of study patients are aged more than 72 hours, with 1.5-2.5 Kg weight, preterm, born at health facility, delivered by normal vaginal mode, of Apgar score of more than 7, having rupture of membrane of less than 24 hours, having no perinatal history of maternal urinary tract infection, their mother were not receives antibiotics and having negative history of chorioamnionitis. As shown in table 3.1.

Table 3.1: Basic information of the study participants.

Variable	Number of Patients	%
Age:		
- Less than 72 hours	85	42.5%
- More than 72 hours	115	57.5%
Gender:		
- Male	109	54.5%
- Female	91	45.5%
Body weight (kilogram):		
- Less than 1.5	69	34.5%
- 1.5 – 2.5	75	37.5%
- More than 2.5	56	28%
Gestational age:		
- Term	61	30.5%
- Preterm	131	65.5%
- Post term	8	4%
Place of birth:		
- Health facility	181	90.5
- Home	19	9.5
Mode of delivery:		
-Normal vaginal delivery	149	74.5%
- Cesarean section	51	25.5%
Apgar score at 5 minutes:		
- Less than 7	49	24.5
- More than 7	151	75.5
Rupture of membrane:		
- Less than 24 hours	171	85.5
- More than 24 hours	29	14.5
Maternal urinary tract infection:		
- Present	11	5.5
- Absent	189	94.5
Antibiotic use:		
-Yes	13	6.5
- No	187	93.5
Chorioamnionitis:		
-Yes	10	5
-No	190	95

Figure 3.1 illustrates numbers and percent of patients whose survive. It's evident that the mortality rate of neonatal sepsis is 41.5%.

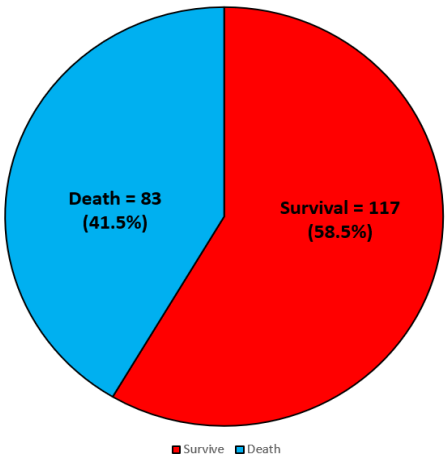

Figure 3.1: Distribution of the study participants according to the survival rate.

Table 3.2 shows comparison between patients whose survive (group A) and those whose passed (group B), regarding different clinical manifestations. Statistically significant difference regarding the presence of lethargy (P value <0.001), vomiting (P value <0.001), respiratory distress (P value <0.001), leukocytes (P value <0.001), elevated blood sugar (P value = 0.029). While not statistically significant differences are present regarding the presence of poor feeding, convulsion, temperature instability, pallor, jaundice, umbilical redness, thrombocytopenia, leukopenia, hemoglobin and C-reactive protein (P value > 0.05) for all.

Table 3.2: Comparison between the two groups regarding different clinical manifestation.

Variable	Group A = 117, (%)	Group B = 83, (%)	P-value
Poor feeding:			
-Yes	61 (52.13%)	45 (54.21%)	0.910
-No	56 (47.87%)	38 (45.79%)	
Lethargy:			
-Yes	41 (35.04%)	42 (50.6%)	**<0.001**
-No	76 (64.94%)	41 (49.4%)	
Vomiting:			
-Yes	29 (24.79%)	39 (46.99%)	**<0.001**
-No	88 (75.21%)	44 (53.01%)	
Convulsion:			
-Yes	16 (13.67%)	10 (12.04%)	0.892
-No	101 (86.33%)	73 (87.96%)	
Temperature instability:			
-Yes	75 (64.1%)	55 (66.26%)	0.878
-No	42 (35.9%)	28 (33.74%)	
Pallor:			
-Yes	31 (26.49%)	21 (25.3%)	0.729
-No	86 (73.51%)	62 (74.7%)	
Jaundice:			
-Yes	66 (56.41%)	47 (56.62%)	0.929
-No	51 (43.59%)	36 (43.38%)	
Respiratory distress:			
-Yes	60 (51.28%)	71 (85.54%)	**<0.001**
-No	57 (48.72%)	12 (14.46%)	
Umbilical redness:			
-Yes	21 (17.94%)	17 (20.48%)	0.392
-No	96 (82.06%)	66 (79.51%)	
Thrombocytopenia:			
-Yes	67 (57.26%)	44 (53.01%)	0.458
-No	50 (42.74%0	39 (46.99%)	
Leucopenia:			
-Yes	30 (25.64%)	19 (22.89%)	0.647
-No	87 (74.36%)	64 (77.11%)	
Leukocytosis:			
-Yes	12 (10.25%)	27 (32.53%)	**<0.001**
-No	105 (89.75%)	56 (67.47%)	
Hemoglobin:			
-Less than 10 g/dl	39 (33.33%)	18 (21.68%)	0.089
- More than 10 g/dl	78 (66.67%)	65 (78.32%)	
Random blood sugar:			
-Normal	65 (55.55%)	31 (37.34%)	
-Low	29 (24.78%)	23 (27.71%)	**0.029**
-High	23 (19.77%)	29 (34.95%)	
CRP:			
-Positive	61 (52.13%0	51 (61.44%)	0.078
- Negative	56 (47.87%)	32 (38.56%)	

Table 3.3 explores risk estimation of different variables, the presence of lethargy, vomiting and respiratory distress are in significant risky association and statistically significant difference for patients whose passed than those whose survived.

Table 3.3: Risk estimation of the study variables.

Variable	Group A	Group B	Odds ratio	Confidence interval	P-value
Age: - < 72 hours - >72 hours	 41 (35.05%) 76 (64.95%)	 44 (53.01%) 39 (46.99%)	0.478	(0.129-1.102)	**0.013**
Delivery: -Normal -CS	 79 (67.52%) 38 (32.48%)	 70 (84.33%) 13 (15.67%)	0.386	0.239-1.039	0.120
Birth weight: - <1.5 Kg - 1.5-2.5 Kg - More than 2.5 Kg	 31 (26.49%) 35 (29.91%) 51 (43.6%)	 38 (45.78%) 40 (48.13%) 5 (6.09%)	 1.0365 Ref 11.520	 0.729-1.348 --- 3.293-16.234	**0.003**
Lethargy: -Yes -No	 21 (17.94%) 96 (82.06%)	 62 (74.69%) 21 (25.31%)	0.074	**0.039-0.138**	**<0.001**
Vomiting: -Yes -No	 23 (19.65%) 94 (80.35%)	 45 (54.21%) 38 (45.79%)	0.206	**0.120-0.590**	**<0.001**
Respiratory distress: -Yes -No	 65 (55.55%) 52 (44.45%)	 66 (79.51%) 17 (20.49%)	0.322	**0.124-0.679**	**0.012**
RBS: -Normal -Low -High	 46 (39.31%) 29 (24.78%) 42 (85.47%)	 50 (60.24%) 23 (27.71%) 10 (12.05%)	 Ref 1.370 10.869	 --- 0.589-1.938 3.293-15.389	**<0.001**

Table 3.4 compares between patients with early onset sepsis and those of late onset sepsis regarding causative micro-organism. *Streptococcus species* founded to be significantly more among patients with late onset sepsis (P value = 0.037).

Table 3.4: Comparison between patients with early and late onset sepsis regarding different causative micro-organisms.

Bacterial type	Early onset sepsis	Late onset sepsis	Total	P- Value
- *Staphylococcus aureus*	42 (41.58%)	59 (58.42%)	101	0.094
- *Streptococcus spp.*	0 (0%)	5 (100%)	5	**0.037**
- *Klebsiella spp.*	35 (53.84%)	30 (46.16%)	65	0.345
-*Pseudomonas spp.*	3 (50%)	3 (50%)	6	1
- *Acinetobacter spp.*	2 (40%)	3 (60%)	5	0.238
Escherichia coli	7 (43.75%)	9 (56.25%)	16	0.339
Serratia spp.	0 (0%)	1 (100%)	1	0.123
Proteus spp.	1 (100%)	0 (0%)	1	0.127

4. DISCUSSION

The fatality rate from neonatal sepsis differs between countries and institutions.[16] Early identification and treatment are essential for reducing the mortality of newborn sepsis. Neonates who are at risk of sepsis must therefore be identified, and if sepsis does occur, it is imperative to quickly identify the traits associated with a poor prognosis.[17]

In this study, the mortality rate of neonatal sepsis is 41.5%, which higher what was found by Carolin Fleischmann et al in his systematic review and meta-analysis.[18] However; antibiotic resistance might the causative factor for such a difference.

Additionally; this study evaluated the major predictors of death in patients with culture-proven sepsis. Lethargy is found to be significantly more among passed group, this is might due to cardiovascular collapse and metabolic derangements, which with goes with Stefani Miranda et al study results.[19] Moreover; the study found that the mortality rate is significantly increased among patients with vomiting and respiratory distress as these events might cause increase in acute inflammatory mediators leading to higher risk of death, these results are parallel to Nour Abdallah Ba-alwi et al.[20] From the other hand; leukocytosis and elevated random blood sugar are linked significantly to death according to this study findings. Oryan Golomb et al also conclude that leukocytosis on the first day of life is a poor predictor of infection.[21] while Badri Kumar Gupta et al found that the mortality rate is higher among the septic newborn with hyperglycemia.[22]

The current study found that streptococcal species is significantly linked to late onset neonatal sepsis, in contrast to other bacterial species with were distributed not significantly between early and late onset sepsis. However; Nour Abdallah Ba-alwi et al. study was showing in significant results[20], anyhow; small sample size can lead to such results.

The study's strength point includes using one hospital setting, guaranteeing consistent records and standard procedures, but also making the data on bacterial profiles and antibiotic resistance not conclusive to the all local community. However, this study has certain limitations because it is retrospective in nature which might affect the clinical evaluations of the patients. Additionally, the study didn't pinpoint the exact moment of the random blood glucose readings, the fact that sure affect the exact finding of random blood sugar relationship to death.

5. CONCLUSION

High antibiotic resistance in Iraq can increase the overall mortality rate of infectious diseases. Moreover; Lethargy, vomiting, respiratory distress, leukocytosis and high random blood sugar are significantly association with death. Following strict protocols and prescribing antibiotics according to culture and sensitivity tests are recommended to all patients with infections regardless to the type and location of infection.

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CONFLICT OF INTERTEST

About this study, the authors disclose no conflicts of interest.

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