PREDICTORS OF MORTALITY OUTCOME IN NEONATAL SEPSIS

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ABSTRACT

A prospective study was carried out to determine the predictors of outcome in neonates with sepsis admitted to neonatal care unit at Basrah Maternity and Children Hospital over six months (from the first of November 2004 till the end of April 2005). One-hundred twenty neonates were studied, sepsis was confirmed by clinical and laboratory measures. Seventy four (61.7%) neonates were males and 46 (38.3%) were females. Thirty three (27.5%) were preterm and 87 (72.5%) were full term. Sixty seven (55.8%) neonates were still alive during period of hospitalization and discharged home, while fifty three (44.2%) neonates died. Early onset sepsis was detected in 35(29.2%) neonates while late onset sepsis was detected in 85(70.8%) neonates, however, the mortality rate was higher in early onset sepsis (62.9%) compared to late onset sepsis (36.5%). The mean body weight was significantly lower in neonates who died (1.97±0.67), compared to those who survived (2.79±0.6). A significantly higher mortality rates were among premature neonates (69.7%), and those with intrauterine growth retardation (70.8%). In addition, the death rate was higher in neonates with maternal history of prolonged rupture of membrane ≥24 hours (61.5%) compared to (39.4%) in neonates with maternal history of rupture membrane of < 24 hours before labor. The clinical signs that predict high mortality were sclermic skin (94.2%), signs of dehydration (82.8%) and prolonged capillary refilling time (68%). Highest mortality was associated with positive blood culture for Pseudomonas aeruginosa and Staphylococcus aureus, where all neonates died (100%), followed by klebsiella spp. and Escherichia coli (71.1%) and (48.5%) respectively in comparison with neonates who have positive blood culture for Proteus and Enterobacter aeruginosa where only 7.9% and 11.1% of neonates died respectively. A statistically significant higher mortality was reported in neonates having thrombocytopenia, neutropenia and C-reactive protein ≥10 mg / dl. Regression analysis of different neonatal and maternal variables, hematological and microbiological tests, revealed that body weight, gestational age, thrombocytopenia, neutropenia, positive blood culture for klebsiella spp., prolonged capillary refilling time, sclerma and signs of dehydration are predictive factors of the outcome of death in neonatal sepsis.

INTRODUCTION

Neonatal infections are a major cause of death worldwide[1]. It is estimated that approximately 4 million deaths occur annually in developing countries in the neonatal period, attributable mostly to infection, birth asphyxia, and consequences of premature birth and low birth weight[2,3] The incidence of neonatal sepsis varies from 1-4 / 1000 live birth in developed countries, to 10-50/1000 live birth in developing countries[4,5]. The incidence of neonatal sepsis varies from nursery to nursery and within the same nursery at different times and depends on conditions predisposing to infection[6]. Risk factors are complex interaction of maternal-fetal colonization, transplacental immunity, and physical and cellular defense mechanisms of neonate[7]. Neonates with sepsis may have either non-specific signs and symptoms or focal signs of infection[4]. The clinical manifestations of infection depend on the virulence of the infecting organism and baby inflammatory response to that agent. The term systemic inflammatory response syndrome (SIRS) is more frequently used to describe this unique process of infection and the subsequent systemic response[4]. The term systemic inflammatory response is used to describe a clinical syndrome characterized by two or more of the following: fever or hypothermia, tachycardia, tachypnea and abnormal white blood cells in immature forms[8]. Sepsis is considered when there is a systemic response to a possible infection[8]. The evaluation of tests for neonatal sepsis is important because the infection may present a very serious threat to the baby. There is an urgent need to know whether the baby has sepsis to institute treatment as early as possible[8]. No single laboratory test has been found to have enough specificity and sensitivity and therefore laboratory confirmation must be used in conjunction with risk factors and clinical signs[5]. These tests include culture of blood, urine and cerebrospinal fluid, leukocyte profile, platelet count, acute phase reactants (ESR, C-reactive protein), latex agglutination tests, or counter immune electrophoreses, and Polymerase Chain Reaction (PCR)[4-7,9]. C-reactive protein (CRP) synthesis increases within (4-6) hrs, doubling every 8 hrs thereafter, and peaking at 36-50 hrs after the onset of inflammation. CRP level remains elevated with

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ongoing inflammation and tissue destruction, but with resolution they decline rapidly because of short half life (4 to 7 hrs), so it parallels the degree of injury and repair, thereby supporting its value as an acute measure of disease activity. CRP is found in serum of normal healthy person in very low concentration < 0.02 mg/dl, in most cases not exceeding 6 mg/dl)[10-13]. Mortality rate from sepsis syndrome depends on definition of sepsis. Reported mortality rate in neonatal sepsis are 10-40% when all bacteremic infections are included in the definition[5]. Anticipation from the clinical history, suspicion from clinical findings and confirmation by preliminary laboratory studies is essential for intact survival of the neonate with sepsis[7]. This study was carried out on neonates with sepsis to compare the epidemiological, clinical and laboratory profiles of neonates with sepsis in relation to outcome (those who survived or died) and to determine the predictors of outcome in patients with neonatal sepsis.

PATIENTS AND METHODS

This is a prospective study, which has been carried out on neonates with sepsis who have been admitted to neonatal care unit at Basrah Maternity and Children Hospital from the first of November 2004 till the end of April 2005. A special questionnaire was designed for the purpose of the study. A total of 120 neonates, their age ranged from (1-28) days with features of sepsis were included in the study (after excluding those with prior antibiotic therapy and neonates with obvious congenital anomalies). The following information were taken:- name, age, sex, date of admission, mode and place of delivery, gestational age (was assessed using Dubowitz criteria)[4], any history of previous hospitalization or history of acute neonatal suffering i.e. any illness occurred during birth or immediately after such as birth asphyxia, respiratory distress which include Respiratory Distress Syndrome (RDS), Transient Tachypnea of the Newborn (TTN) and meconium aspiration. Data regarding maternal history of prolonged rupture of membrane (and its duration), fever, antibiotic use and urinary tract infection (UTI) were also recorded. After history and clinical examination of neonates included in the study, clinical features regarding signs and symptoms of sepsis like: poor feeding, lethargy, coffee-ground vomiting, diarrhea, oliguria, convulsion, temperature instability, pallor, jaundice, cyanosis, tachycardia, apnea, respiratory distress, signs of dehydration, signs of intrauterine growth retardation ,mottled skin, sclerma, omphalitis, hepato-splenomegaly and abdominal distension and were also recorded. A capillary refilling time was assessed for these neonates, a time ≥3 seconds is considered prolonged i.e. delay capillary refilling indicates poor perfusion or shock state[4]. The outcome of each neonate was recorded on discharging from neonatal nursery unit, and neonates with sepsis were grouped into those who survived and those who died. A sample of 0.5 ml of blood was taken for estimation of haemoglobin, total white blood cell, absolute neutrophil count and platelets count. A sample of at least 2ml of blood per set was taken from peripheral vein from 2 separate sites after adequate skin disinfection using iodine solution that left to dry and then wipped off with (70%) alcohol, both samples were taken before antibiotic administration, samples were cultured aerobically and anaerobically. C-reactive protein has been measured in 100 neonates only; 0.5 ml of blood was collected in a plain tube without EDTA and was used for estimation of CRP by latex-agglutination test. The cutoff value for CRP $\geq$ 10mg/dl [4,5,10-13] was used to compare between the neonates with sepsis and the outcome.

Statistical analysis: Statistical analysis was done using SPSS package, data were expressed as mean $\pm$ SD, comparison of proportions was performed using Chi-square and exact Fisher's test, P-value of less than 0.05 was considered as statistically significant, P-value <0.01 as highly significant and P-value <0.001 as extremely significant. Logistic regression analysis was done for all the variables used for the comparison of the neonates included in the study in relation to the outcome.

RESULTS

A total 120 neonates with sepsis aged (1-28) days were included in the study. Sixty seven (55.8%) neonates were still alive and discharged home and fifty three (44.2%) died during period of hospitalization, the characteristics of neonates studied are illustrated in *(Table-1)*. A statistically significant higher percent of death was reported in neonates with early onset sepsis (62.9%) compared to (36.5%) in neonates with late onset sepsis (P<0.001). The mean body weight was significantly lower in neonates with sepsis who died; the frequency of death was also significantly higher in preterm babies, babies with IUGR, babies with previous hospitalization, babies that have been delivered at home and history of acute suffering especially with respiratory distress.

Table 1. ***Outcome of neonates with sepsis in relation to selected neonatal variables***

Variables		Outcome		P-value
		Alive (67) No. (%)	**Deceased (53)** No. (%)	
Age (days)	*< 7 days (No.35)*	13 (37.1)	22 (62.9)	< 0.001
	7-28 days (No.85)	54 (63.5)	31 (36.5)	
Sex	*M (No.74)*	42 (56.75)	32 (43.25)	> 0.05
	F (No.46)	25 (54.34)	21 (45.66)	
Bwt (kg)	*Mean ± SD*	2.79 ± 0.60	1.97 ± 0.67	< 0.001
	(Range)	(1.5 - 4.00)	(1.25 - 5)	
Gestational age	*Preterm*	10 (30.3)	23 (69.7)	< 0.001
Term	*Appropriate to age*	50 (79.36)	13 (20.64)	
	IUGR	7 (29.2)	17 (70.8)	
Type of delivery	*VD*	62 (56.4)	48 (43.6)	> 0.05
	C / S	5 (50)	5 (50)	
Site of delivery	*Hospital*	63 (63)	37 (37)	< 0.001
	Home	4 (20)	16 (80)	
Previous Hospitalization	*Yes*	5 (15.6)	27 (84.4)	< 0.001
	No	62 (70.46)	26 (29.54)	
Acute suffering	*Resp. distress*	3 (12)	22 (88)	< 0.001
	Birth asphyxia	2 (66.7)	1 (33.3)	
	No	62 (67.4)	30 (32.6)	

History of prolonged rupture of membrane (PROM), maternal use of antibiotics, maternal fever and UTI in the third triamester was studied and the results are presented in *(Table-2)*. There was a significant association between the outcome of neonates with sepsis and the PROM and maternal fever (P<0.001). This table also reveals that there was no significant association between the outcome of neonates with sepsis and the maternal antibiotic use and UTI (P>0.05).

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Table 2. ***Outcome of neonates with sepsis in relation to selected maternal variables***

Variables		Outcome		P- value
		Alive (67) No. (%)	**Deceased (53)** No. (%)	
ROM	*< 24 hrs.*	57 (60.6)	37 (39.4)	< 0.001
	≥ 24 hrs.	10 (38.5)	16 (61.5)	
Antibiotic Use	*Yes*	7 (53.8)	6 (46.2)	> 0.05
	No	60 (56.1)	47 (43.9)	
Fever	*Present*	11 (32.4)	23 (67.6)	<0.001
	Absent	56 (65.1)	30 (34.9)	
UTI	*Yes*	33 (54.1)	28 (45.9)	> 0.05
	No	34 (57.6)	25 (42.4)	

The symptoms of sepsis that the neonates presented with were compared with outcome and results are illustrated in *(Table-3)*. This table shows that there was a statistically significant association between poor feeding, lethargy and coffee ground vomiting with the outcome, while no significant association was detected between the outcome and other symptoms.

Table 3. ***Outcome of neonates with sepsis in relation to neonatal symptoms***

Symptoms		Outcome		Total	P- value
		Alive (67) No. (%)	**Deceased (53)** No. (%)		
Poor feeding	*Present*	43 (47.8)	47 (52.2)	90	< 0.001
	Absent	24 (80)	6 (20)	30	
Diarrhea	*Present*	12 (80)	3 (20)	15	> 0.05
	Absent	55 (52.4)	50 (47.6)	105	
Vomiting (coffee-ground)	*Present*	4 (23.5)	13 (76.5)	17	< 0.05
	Absent	53 (51.5)	50 (48.5)	103	
Convulsion	*Present*	2 (40)	3(60)	5	> 0.05
	Absent	65 (56.5)	50 (43.5)	115	
Oliguria	*Present*	4 (57.1)	3 (42.9)	7	> 0.05
	Absent	63 (55.8)	50 (44.2)	113	
Lethargy	*Present*	29 (42.02)	40 (57.98)	69	< 0.001
	Absent	38 (74.50)	13 (25.50)	51	

The clinical signs noted in neonates with sepsis were also compared with the outcome, *(Table-4)*. There was a significant association between outcome and many signs including signs of dehydration, hypothermia, cyanosis, apnea, respiratory distress, prolonged capillary refilling time, pallor, sclerma, mottled skin and petecheal rash.

Table 4. ***Outcome of neonates with sepsis in relation to clinical signs***

Signs		Outcome		P- value
		Alive (67) No. (%)	Deceased (53) No. (%)	
Signs of Dehydration	*present*	6 (17.2)	29 (82.8)	< 0.001
	absent	61 (71.76)	24 (28.24)	
Hypothermia	*present*	4 (23.5)	13 (76.5)	< 0.01
	absent	63 (61.1)	40 (38.9)	
Fever	*present*	13 (76.5)	4 (33.5)	> 0.05
	absent	54 (52.4)	49 (47.6)	
Cyanosis	*present*	3 (25.0)	9 (75.0)	< 0.05
	absent	64 (59.2)	44 (40.8)	
Apnea	*present*	0 (0.0)	7 (100)	< 0.001
	absent	67 (59.3)	46 (40.7)	
Respiratory Distress	*present*	25 (43.10)	33 (56.9)	< 0.01
	absent	42 (67.7)	20 (32.3)	
Full Fontanel	*present*	1(16.7)	5 (83.3)	> 0.05
	absent	66 (57.9)	48 (42.1)	
Capillary Refilling	*normal*	43 (95.6)	2 (4.4)	< 0.001
	prolonged	24 (32.0)	51 (68)	
Tachycardia	*present*	39 (56.5)	30 (43.5)	< 0.05
	absent	28 (54.9)	23 (45.1)	
Pallor	*present*	11 (39.29)	17 (60.71)	< 0.05
	absent	56 (60.87)	36 (39.13)	
Jaundice	*present*	11 (61.11)	7 (38.89)	> 0.05
	absent	56 (54.9)	46 (45.1)	
Petecheal rash	*present*	0 (0.0)	5 (100)	< 0.05
	absent	67 (58.3)	48 (41.7)	
Sclerma	*present*	2 (5.7)	33 (94.3)	< 0.001
	absent	65 (76.5)	20 (23.5)	
Abd. Distension	*present*	2 (28.5)	5 (71.5)	> 0.05
	absent	65 (57.5)	48 (42.5)	
Hepato - splenomegaly	*present*	2 (40.0)	3 (60.0)	> 0.05
	absent	65 (56.5)	50 (43.5)	
Omphalitis	*present*	5 (35.7)	9 (64.3)	> 0.05
	absent	62(58.5)	44 (41.5)	
Mottled Skin	*present*	21 (35)	39 (65.0)	< 0.001
	absent	46 (76.7)	14 (22.3)	

Klebsiella was the commonest bacteria isolated in 38(36.6%), followed by *E. coli* 33(27.5%), and *E.aeruginosa* 27(22.5%). Other bacteria were *Proteus* in 13(10.8%), group B *streptococc*i, *Staphylococcus aureus* and *Pseudomonas aeruginosa* in 3 neonates for each (2.5%), *(Table-5)*

Table 5. ***Outcome of neonates with sepsis in relation to results of blood culture.***

Bacteria	Total	Outcome	
		Alive (67) (No.) (%)	Deceased (53) (No.) (%)
E. coli	33	17 (51.5)	16 (48.5)
E. aeruginosa	27	24 (88.9)	3 (11.1)
gp B. streptococci	3	3 (100)	0 (0.0)
K- pneumoniae	38	11 (28.9)	27 (71.1)
P. aeruginosa	3	0 (0.00)	3 (100)
Proteus	13	12 (92.31)	1 (7.69)
Staph. aureus	3	0 (0.00)	3 (100)

P- Value < 0.001

The results of hemoglobin level, white blood cells and platelets counts are presented in *(Table-6)*. The mean hemoglobin, platelets, WBC and ANC level were significantly lower in neonates with sepsis who died compared to those who survived, this table also reveals that a significantly higher number of neonates with sepsis who died had a CRP level ≥10mg/dl (77.5%) compared to neonates who survived, and the difference was statistically extremely significant.

Table 6. ***Outcome of neonates with sepsis in relation to hematological variables***

Variables*	Outcome		P- value
	Alive	Deceased	
Hb* (g /dl)	11.8 ± 2.3	8.79 ± 1.4	< 0.001
Plt* (cell / mm^3)	136.402 ± 57.39	97.566 ± 28.7	< 0.001
WBC*(cell / mm^3)	8171.64 ± 6419.9	4509.4 ± 2883.3	< 0.001
ANC* (cell / mm^3)	2367.61 ± 3762.3	676.43 ± 595.9	< 0.05
CRP* < 10 mg/dl ≥ 10 mg/dl	36 (94.7) 14 (22.5)	2 (5.3) 48 (77.5)	< 0.001

***Values were expressed as mean ± SD**
***For CRP data were reported as No. (%)**

The whole variables included in the study were subjected to logistic regression analysis to know which variables are positively correlated with poor prognosis or death among neonates with sepsis; the variables which are correlated with death outcome are presented in *(Table-7)*. It was observed that the presence of prematurity, IUGR, low birth weight, thrombocytopenia, neutropenia, positive blood culture for *K.pneumoniae*, prolonged capillary refilling time, sclerma and signs of dehydration proved to be significant factors predicting the risk of death in neonates with sepsis.

Table 7. ***Logistic regression analysis of the variables use to compare the outcome of neonates with sepsis***

Variables	B*	SE*	Significant
B. weight (kg)	- 1.1231	0.5437	< 0.05
Gestational age	1.5256	0.5070	< 0.001
PIT (cell / mm^3)	- 2.6E – 05	1.155E – 05	< 0.05
ANC (cell / mm^3)	- 0.0018	0.0005	< 0.001
K. pneumoniae	- 1.0874	0.4577	< 0.001
Prolonged cap. refilling time	6.3524	1.6417	< 0.001
Sclerma	- 3.3469	1.1201	< 0.001
Signs of dehydration	- 2.6012	1.2121	< 0.05

B*: regression coefficient. SE*: standard error

DISCUSSION

Neonatal mortality rate is a reliable yardstick for evaluating the overall progress of perinatal care in a community. Knowledge of local or regional health problems is a prerequisite for establishing an effective health care delivery system[14]. Comprehensive statistical information regarding neonatal death is the basis for developing a sound program for the early detection of the syndrome of neonatal wastage, along with the ability to assess treatment and outcome[14]. Neonatal sepsis may have subtle, diverse and non specific symptoms and signs, moreover, a delay in the diagnosis and commencement of treatment result in a high morbidity and mortality rates[12]. Since our neonatal unit is a referral unit, it attracts mainly the high risk patients and so in this study a high mortality rate was reported about (44.2%), the same high result was reported in Basrah (Iraq) by Radhy H. in 2001 (43.5%)[15], similar results were obtained in Abha (Saudia Arabia) by Asindi A et al, (44%)[16] and by Rodriguez-weber, et al in Mexico (43.9%)[17], while lower mortality rates were detected by other authors as that carried out by Ezechukwze C, et al in Nigeria (19.3%)[18], by Koutouby A et al, in UAE (26%)[19], Stall B. in USA (28%)[20], and by Dawodu A et al, in Al-Dammam (Saudi Arabia)

(28%)[21], these differences in mortality rate in neonatal sepsis among different countries may be explained by many factors e.g: socio-economic, geographical and racial factors, use of ventilators, incubators, different micro-organisms and use of different antibiotics[19]. The percent of mortality in early onset sepsis was (62.5%) and it was higher than in late onset sepsis (36.5%), a similar result was found in other studies[17,22]. Although other studies reported that the mortality rate is higher in late onset sepsis[15,21,23], the early onset sepsis is mainly related to maternal genitor-urinay tract infection while late onset sepsis is mainly related to invasive diagnostic procedures, prolonged hospitalization and prolonged antibiotic use.

In this study there was no statistically significant difference in the frequency of death among both sexes, a similar result was obtained by Rodriguez M et al, in study carried out in Mexico[17] and also by a study carried out in Dubia by Koutouby A[19], although other studies reported a higher percent of death among males with sepsis[21,24] suggesting the possibility of sex linked factors in host susceptibility. This study illustrated that low birth weight LBW (IUGR & prematurity) were risk factors for death outcome in neonates with sepsis, a result similar to many previous studies carried in different countries whether developing and developed world[16,17,19-21], a factor related to inherent immunological deficiency, or because these neonates need prolonged hospitalization which increases risk of nosocomial infection. A significantly higher percent of death was reported among neonates with sepsis who had a history of previous hospitalization; these neonates were at a greater risk of acquiring nosocomial infection. An ill neonates who are subjected to various procedures get breach in their host defense mechanism, either mechanically or immunologically[25]. A higher percent of death was reported among neonates with sepsis who had a history of acute illness during the first few days of life such as respiratory distress due to different causes or birth asphyxia, a result in agreement to that reported in Mexico[17], and Saudi Arabia[21], may be because this group of patients needs prolonged hospitalization and many invasive procedures that predispose them to infection more. The death outcome was higher in neonates with sepsis whose mothers had prolonged rupture of membrane ($\geq$ 24 hrs) and fever, other studies showed that the duration of PROM $\geq$18 hrs was associated with increased risk of mortality in neonatal sepsis[22], and other studies reported also that a duration of rupture of membrane $\geq$ 24 hrs increases risk of death in neonatal sepsis[19,21]. However, in a study carried by in Saudia Arabia by Asindi A et al[16], didn't demonstrate any role for the duration of rupture membranes in the outcome of neonates with sepsis. Among the clinical signs and symptoms: poor feeding, lethargy, coffee-ground vomiting, respiratory distress, signs of dehydration, hypothermia, pallor, cyanosis, apnea, mottled skin, sclerma & prolonged capillary refilling time, reported significant association with outcome of death in neonatal sepsis, a similar result was reported by other study[17]. Gram negative microorganisms were the most common microorganisms isolated from those neonates with sepsis; especially *Klebsiella pp*. while low incidence of *gp.B.hemolytic Streptococci* was reported. The mortality was higher in neonates whose blood culture were positive for *P.aeruginosa* (100%), *Staphylococcus aureus* (100%) followed by *klebsiella* (71.1%) & *E.coli* (48.5%). Similar results were obtained by many studies in Mexico[17], Iraq[15,26], Saudi Arabia[16,24], and Dubai[19]. All these studies showed a higher incidence of gram negative micro-organisms among neonates with sepsis who died compared to those who survived. Hematological findings including Hb, WBC, ANC and PLT have been studied, the current study showed that the mortality rate is higher when neonates have anemia, thrombocytopenia, leukopenia and neutropenia; a similar result was reported in previous studies[12,17]. Thrombocytopenia was reported to be more severe with gram negative sepsis and fungal infection, the mechanism is a combination of diffuse endothelial injury, bacterial/fungal toxins, increased platelet activation and DIC[27]. The frequency of death was higher in those neonates with C-reactive protein level $\geq$ 10 mg/dl compared to neonates with a CRP level < 10 mg/dl. This in agreement to other study[10,13],although other studies showed a CRP level of > 6mg/dl as a risk factor for increasing mortality in neonatal sepsis[11,12]. Although essential for diagnosis and appropriate

management, blood culture results are not immediately available and their yield is low, although non-specific for neonatal sepsis, CRP has the highest sensitivity, specificity and high negative and high positive predictive values[12]. After subjecting all data for logistic regression analysis, the predictive factors for death were gestational age, birth weight, thrombocytopenia, neutropenia, positive blood culture for *klebsiella spp*, sclerma, signs of dehydration and prolonged capillary refilling time. Neonatal sepsis remains a major cause of mortality in this age group. As there is a trend of changing pattern of organisms responsible for bacterial infection in the newborn. The possible changing nature of the bacterial pathogen at the neonatal unit needs further monitoring and periodic surveillance, and there is a need to establish and review local antibiotic sensitivities of pathogens for optimal therapy. With early diagnosis and treatment, introduction of new antibiotics and increased awareness of proper hand washing practice, the neonatal mortality and morbidity can be reduced markedly.

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