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A study on the outcome of neonates with sepsis at the Lagos University Teaching Hospital

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ABSTRACT

Background: Neonatal morbidity and mortality are major public health challenges in our local environment with a huge percentage of deaths in the neonatal period attributable to sepsis. **Aim:** The aim of the study was to assess the factors that affect patients' outcome with respect to sepsis in neonates. **Methods:** This was a prospective descriptive cross sectional study. Neonates with proven and suspected sepsis were recruited into the study. Outcome was assessed based on the length of hospital stay and mortality. Clinical response to treatment was also assessed. **Results:** Nine factors were identified as risk factors for mortality, birth weight (< 2500g *P* = 0.000, OR = 7.214, CI = 2.5 – 21.0), prolonged rupture of membranes (PROM) (*P* = 0.014, OR = 2.470, 95% CI = 1.2 -5.1), prolonged preterm rupture of membranes (PPROM) *P* = (0.046. OR = 2.1, 95% CI = 0.9 -4.6) multiple gestation (*P* = 0.009), an infectious clinical diagnosis (*P* = 0.046, OR = 0.480), frequent changes in antibiotics (*P* = 0.013). Others were a low Apgar score (*P* = 0.000), presence of organisms in intravenous fluids (*P* = 0.042, OR = 0.2, 95% CI = 0.02 – 1.3 and the presence of organisms in the blood stream (*P* = 0.007). **Conclusion**: This study determined the mortality rate in our environment due to sepsis to be 15.7%. Risk factors for a poor outcome include low birth weight, perinatal period, and maternal illness in pregnancy and isolation of a pathogen from the blood stream.

Key words: Neonatal sepsis, prolonged stay, mortality, bactec 9050, microbact 12a, risk factors

INTRODUCTION

Neonatal morbidity and mortality are major public health challenges in our local environment with a huge percentage of deaths in the neonatal period attributable to sepsis. It is estimated that 98.5% of neonatal mortality occurs in developing countries with neonatal sepsis directly responsible for 26% of deaths.[1] Neonatal sepsis in itself is potentially treatable and preventable however despite considerable advances and improvements in the survival

rates of the newborn in developed countries, there has not been a concomitant improvement in outcomes recorded in developing countries.[1]

The neonatal period is the most vulnerable period of life due to susceptibility to infectious agents. Neonates are known to be deficient in humoral and cell mediated immunity due to the relative immaturity of their immune systems and non-exposure to infections agents and in addition studies have proven that they produce immunoglobulins at a lower rate when compared to adults.[2]

In utero, transplacental maternal antibodies of the immunoglobulin G (IgG) type mediate humoral immunity primarily, as this is the only class of immunoglobulins that is capable of crossing the placenta.[3] As a result, low and very low birth weight neonates and preterm neonates are less likely to receive sufficient amounts of IgG compared to term infants. In addition, T cell function is less efficient in neonates and this predisposes them to various infetions.[4] The ecologic niche of organisms responsible for neonatal sepsis has continuously been evolving over time resulting in changes in the prevalence of organisms in various hospitals. These pathogens have developed increased resistance to the various antimicrobials.[5]

METHODOLOGY

Study design and location

The study was carried out at the neonatal unit of the Lagos University Teaching Hospital (LUTH), Idi-araba. This hospital is a 761 bed facility located in an urban cosmopolitan setting. The neonatal unit of the hospital has a total bed space of 73 and is divided into four wards - Neonatal Unit (NNU), Wards D1 (Neonatal unit for babies delivered outside LUTH), Children Emergency Room (CHER) and E4 (In patient surgical pediatric ward). The NNU serves neonates delivered to booked mothers in the hospital while D1, CHER and E4 serve neonates delivered outside the hospital to un-booked mothers. The total bed space of NNU is 38 patients while that of D1 is 35.

Patients were followed up to the time of discharge, demise or up to two weeks of discharge to the outpatient clinic. Outcome was assessed based on mortality rates, length of hospital stay, response or otherwise to antimicrobial agents and resolution or otherwise of clinical features

Sample size

The average isolation rate of aerobic bacteria from manual blood culture systems is approximately 20% [6]

Using the prevalence figure incalculating the sample size[7]

$$N = \frac{Z^2Pq^7}{d^2}$$

Where Z = Critical value at 95% confidence level set at 1.96

d= is the precision set at 5%

P is the proportion of the population that have positive yield from blood culture. P is set at 20%

Sample size = 1.96x1.96x0.2x0.8/0.05x0.05 = 245.56

The sample size for the study will therefore be set at 250

Recovery of organisms

Two venous blood samples were taken 1 hour apart via phlebotomy from the antecubital fossa, fore arm or the hands of the neonates aseptically, applying universal precautions. The volume of blood withdrawn was 1 to 3millitres. Blood obtained from each neonate was aseptically dispensed into the BACTEC Peds Plus aerobic blood culture bottle. Bottles flagged as positive by the system were removed, Gram stained and sub cultured onto appropriate media such as blood, chocolate and Mac Conkey agar. Chocolate agar was incubated in 5% CO_2 while blood and Mac Conkey agar were incubated in ambient air.Incubation was at 37^0C for 18 to 24 hours

Gram negative organisms were identified with the Microbact 12E/24E identification system.

Ethical considerations

Approval was obtained from The Ethics and Research committee of The Lagos University Teaching Hospital. Informed consent was obtained from the parents and/or caregivers of the neonates before the filling of questionnaires.

Statistical analysis

A structured questionnaire considering medical, surgical, obstetric and antibiotic history was given to patient's relatives/caregivers to fill in order to identify

and assess risk factors. Data obtained from the questionnaires was analyzed with EPI-INFO 3.6.1 software version 2008 and SPSS version 21.0 by cross tabulation of risk factors and univariate/multivariate analysis with data from the laboratory results. The data was presented with frequency tables, charts and summary statistics. Also analysis was done with chi square, 95% confidence interval and odd ratio. The *P*-value was set at a value < 0.05.

RESULTS

The predominant organisms isolated from the blood stream of neonates were *Klebsiella pneumoniae* [n = 31 (36.5%)] followed by *Staphylococcus aureus*n [n= 16 (18.8%)] (table 1).

There were three possible outcomes for patients – died, discharged and increased length of hospital stay. Nine factors were identified as risk factors for mortality, birth weight (< 2500g *P* = 0.000, OR = 7.214, CI = 2.5 – 21.0), prolonged rupture of membranes (PROM) (*P* = 0.014, OR = 2.470, 95% CI = 1.2 -5.1), prolonged preterm rupture of membranes (PPROM) *P* = (0.046. OR = 2.1, 95% CI = 0.9 -4.6) multiple gestation (*P* = 0.009), an infectious clinical diagnosis (*P* = 0.046, OR = 0.480), frequent changes in antibiotics (*P* = 0.013). Others were a low Apgar score (*P* = 0.000), presence of organisms in intravenous fluids (*P* = 0.042, OR = 0.2, 95% CI = 0.02 – 1.3 and the presence of organisms in the blood stream (*P* = 0.007) (table 2).

Findings from the results of outcome with respect to mortality show that babies that were low birth weight were 7.2 times more likely to die compared to those who were appropriate for birth weight. It was also observed that babies that had PROM were 2.5 times more likely to die. For those who had organisms recovered from their intravenous fluids they were 0.2 times more likely to die.

Further logistic multivariate regression analysis showed the birth weight to be the single most important risk factor for neonatal sepsis *P* = 0.001, OR = 7.179, CI = 23.104 – 2.239) (table 3).

With respect to increased length of hospital stay two risk factors were identified – maternal illness in pregnancy *P* = 0.030 and multiple gestation *P* = 0.034 (table 4).

DISCUSSION

Numerous studies have reported that the most common pathogens isolated in early onset sepsis include: *Group B Streptococci* (which was not found in the study) *Staphylococcus aureus*, *Escherichia coli* (also not seen) *Klebsiella species* and *Listeria monocytogenes.*[8,9] The data from this study shows that the pattern of bacterial isolates differ in our local center and therefore the use of different antibiotic guidelines based on local susceptibility data will be warranted. There is therefore the need to formulate local guidelines that will aid in the rapid identification of at risk neonates especially those who have developed sepsis and develop treatment modules that will help to reduce mortality in our local center to the barest minimum.

The length of hospital stay was not seen to increase susceptibility to sepsis, possibly due to observance of infection control protocols on the wards by the pediatricians and the involvement of clinical microbiologists in the management of these neonates. Likewise there was no association seen between the diagnosis at presentation and length of hospital stay, or the length of stay at the referral hospital before coming to the hospital and the number of days on admission.

The mortality rate of the study was 15.7%. This mortality rate is comparable to a figure of 19.8% seen in an Iranian study and demonstrates the relatively high disease burden of neonatal sepsis in our environment.[10] A strong statistical association was seen between age and survival outcome, with those younger than seven days having a higher mortality rate than those greater than seven days which is expected considering lower birth weights and diminished immune response in the younger age group. These findings are also in line with a similar study in Iran which reported a higher mortality figures for younger babies.[11] A similar relationship was also seen with birth weight where 89.7% of those who died were low birth weight (<2500g) as against 10.3% for those greater than 2500g.

Table 1: Aetiologic agents of sepsis in neonates at Lagos University Teaching Hospital

Organism	**N (%)**
Acinetobacterbaumanii	3 (3.5)
Acinetobacteriwofii	1(1.2
Bukholderiacepacia	6 (7)
Candidaalbicans	1 (1.2)
Coagulase Negative Staphylococci	10 (11.8)
Enterococcus species	6 (7)
Klebsiellaoxytoca	3 (3.5)
Klebsiellapneumoniae	31 (36.5)
Proteus vulgaris	4 (4.7)
Staphylococcusaureus	16 (18.8)
Serratiarubideae	4 (4.7)
Total	**85 (100)**

Table 2a: Risk factors for mortality in neonates with suspected sepsis n (%)

Risk factors		Died	Discharged	p-value		Odds Ratio	95% CI
Birth weight							
	<2500g	35 (89.7)	114 (54.8)	0.000		7.214	2.5 - 21.0
	>2500g	4 (10.3)	94 (45.2)				
PROM							
	Yes	15 (38.5)	42 (20.8)	0.014		2.475	1.2 -5.1
	No	24 (61.5)	166 (79.8)				
PPROM							
	Yes	12 (30.8)	36 (17.3)	0.046		2.123	0.9 – 4.6
	No	27 (69.2)	172 (82.7)				
Gestational type							
	Singleton	29(13.6)	184 (86.4)		0.009	-	-
	Twins	10 (34.5)	19 (65.5)				
	Quintuplets	0 (0)	5 (100)				
	EMCS	11 (14.9)	63 (85.1)				
	ELCS	1 (5.9)	16 (94.1)				
	Instrumental delivery	1 (20)	4 (80)				
Clinical diagnosis							
	Infectious	27 (20)	108 (80)	0.046	0.480	-	
	Non infectious	12 (10.7)	100 (89.3)				
Number of antibiotic switches							
	0	27 (15.8)	144 (84.2)	0.013	-	-	
	1	12 (16.9)	59 (83.1)				
	2	0 (0)	100 (5)				

Table 2b: Risk factors for mortality in neonates with suspected sepsis n (%)

Risk factors		Died	Discharged	*p*-value	Odds Ratio	95% CI
APGAR						
	High risk	83 (33.3)	167 (66.7)	0.000	-	-
	Intermediate	25 (10)	225 (90)			
	Low risk	15 (6.1)	235 (93.9)			
Organisms from IV fluid						
	No growth	27 (17.4)	180 (82.6)	0.041	0.17	0.02 - 1.3
	Growth	1 (2.6)	38 (97.4)			
Organisms isolated from the blood stream						
Gram negative isolates						
	A baumanii	2 (67.3)	1 (33.3)	0.007		
	A iwofii	0 (0)	1 (100)			
	B cepacia	1(20)	4 (80)			
	K oxytoca	0 (0)	1(100)			
	K pneumonia	1 (3.2)	30 (96.8)			
	P vulgaris	0 (100)	4 (100)			
Gram positive isolates						
	CONS	1 (10)	9 (90)			
	S aureus	3 (6.7)	13 (93.3)			
	Enterococcus species	1 (16.7)	(83.3)			
Fungal isolate						
	Candida albicans	1 (100)	0 (0)			

Table 3: Independent risk factor for mortality in neonates due to sepsis

Variable	B	S.E	Wald	Df	Sig	Exp (B)	95%CI for Exp (B)	
							Lower	Upper
PROM	-0.110	0.506	0.047	1	0.828	0.896	0.332	2.417
PPROM	-0.670	0.538	1.549	1	0.213	0.512	0.178	1.470
Birth weight	1.971	0.594	10.997	1	0.001	7.179	2.239	23.014
Age	0.620	0.423	2.149	1	0.143	1.858	0.812	4.256
MSAF	-0.130	0.754	0.029	1	0.864	0.879	0.200	3.853
Instrumentation	-0.172	0.442	0.152	1	0.696	0.842	0.354	2.000
Birth status	-0.426	0.383	1.236	1	0.266	0.653	0.308	1.384
Maternal illness	-0.943	0.492	3.672	1	0.055	2.567	0.979	6.731

Table 4: Risk factors for prolonged hospital stay in neonates with suspected sepsis

Risk factor		< 7 days	8-14 days	>14 days	*P*- value
Maternal illness					
	Absent	**88 (44)**	**74.5 (41)**	**69 (100)**	**0.030**
	Present	**12 (6)**	**25.5 (14)**	**31 (45)**	
Ward					
	NNU	19.4 (24)	24.2 (30)	56.5 (70)	
	D1	19.6 (21)	19.6 (21)	60.7 (65)	
	CHER	29.4 (5)	23.5 (4)	47.1 (8)	
	E4	0 (0)	0 (0)	100 (2)	
Type gestation					
	Singleton	**18.7 (40)**	**24.8 (53)**	**56.5 (121)**	**0.034**
	Twin	**32.3 (10)**	**6.5 (2)**	**61.3 (19)**	
	Quintuplet	**0.0 (0)**	**0.0 (0)**	**3.4 (5)**	

With respect to those who had organisms isolated from them 9.6% died, while 90.4% were discharged. The high discharge rate could be due to aggressive antibio-therapy and the increased use of laboratory results in guiding therapy by clinicians.

Maternal illness in pregnancy was identified as a risk factor for prolonged hospital stay; as those babies born to mothers with such a history had a tendency to stay longer on admission. 69.2% of those who stayed greater than fourteen days on admission were born to mothers who had a maternal illness in pregnancy. The relatively high rate of early onset sepsis detected in this study, provides a reservoir of infectious neonates who pose a considerable risk of nosocomial transmission to other neonates. It may therefore be essential to conduct more studies on the bacterial colonization patterns of the maternal genital tract and the possible role of intra-partum antibiotic prophylaxis in order to aid in bringing about a reduction in the incidence of early onset sepsis.

Numerous studies have reported that the most common pathogens isolated in early onset sepsis include: *Group B Streptococci* (which was not found in the study) *Staphylococcus aureus*, *Escherichia coli* (also not seen) *Klebsiella species* and *Listeria monocytogenes.*[8,9] The data from this study shows that the pattern of bacterial isolates differ in our local centre and therefore the use of different antibiotic guidelines based on local susceptibility data will be warranted.

There is therefore the need to formulate local guidelines that will aid in the rapid identification of at risk neonates especially those who have developed sepsis and develop treatment modules that will help to reduce mortality in our local center to the barest minimum.

The presence of Premature Rupture of Membranes (PROM) was also seen to negatively impact on outcome. A substantial figure; 38.5% of neonates with PROM died highlighting the importance of this clinical entity on neonatal mortality in our environment. However PROM or foul smelling liquor did not increase length of admission of neonates as opposed to some other studies.[11]

As would be expected neonates who had pathogens recovered from their blood stream were two and a half times more likely to die when compared to neonates who had no pathogens found. These sub population of neonates were also more likely to stay longer in the hospital. The clinical diagnosis was found to impact on patient outcome. Surprisingly patients with an infectious diagnosis (n=112) were less likely to die than those with a non-infectious condition (n=135). This is probably due to the severity of some non-infectious illnesses such as congenital heart disease, hypoxic ischemic encephalopathy and multiple congenital anomalies which are not amenable to antimicrobial therapy.[13]

The relationship between parental anthropometrics and birth weight may be used as a screening tool in the identification of at risk low birth weight babies after birth in our local tertiary hospitals in the future.[14]

Frequent changes in antimicrobial therapy was not seen to impact patient outcomes as evidenced by the number of participants who had changes in therapy (n= 79). The reason for this might be the increased use of the microbiology teams' presence, availability of suggestions in susceptibility data and the fact that results came out faster than occurred previously with the manual glucose broth system. However a larger multi-centre study may be needed to validate the effect of frequent changes in antimicrobials on patient outcome.

CONCLUSION

Findings from the study revealed that the mortality rate due to sepsis in our environment is 15.7%. Risk factors for poor outcome include low birth weight, perinatal period, maternal illness in pregnancy and isolation of a pathogen from the blood stream. The identification and use of these factors will help to form a frame work for those who may be at risk of acquiring sepsis and help improve outcome in those who are identified early at being at risk of sepsis.

RECOMMENDATIONS

Neonates who present with signs and symptoms of neonatal sepsis need to be

monitored acutely in order to reduce mortality to the barest minimum. Aggressive antibiotherapy is essential in the management of neonatal sepsis in our local environment with potent antimicrobials and a scaling down after response to therapy.

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